

Trigeminal Neuralgia has different tolerance to these medications and to his/her pain, but , over the years of disease progression, at least half will eventually find that medications do not adequately control their progressively worsening TN.

Medication has not been shown to slow the progression of the disease. On the contrary, over the years, most people often find themselves having to take higher doses of medication or having to take several different medications together to control their pain with a resultant accumulation of frequent problematic side effects. Eventually, over the long term, about half of all Trigeminal Neuralgia patients will seek a surgical solutions to manage there pain.

Surprisingly, the latest scientific work has shown that the likely cause of this terrible pain is a tiny nerve lesion measuring less then 0.5 cm!

Equally surprising is the fact that this small injury to the nerve appears in many cases to be highly reversible even in cases that have lasted many years and become severely problematic.

Ultrasound is sound that is not audible. Ultrasound delivered to injured nerves has been shown in several studies to heal the type of nerve damage commonly seen in the trigeminal nerve of patient's with Trigeminal Neuralgia. Until the Painshield technology came to light, there was no available ultrasound device that could safely deliver healing ultrasound waves to the inside of the skull where the lesion of the trigeminal nerve is located.

Today, the amazing results seen in patients with trigeminal neuralgia who have been treated with the Painshield demonstrate that there is definitely a role for this healing sound in the treatment of trigeminal neuralgia. Firstly, for the rapid and impressive pain relief obtained with this technology. But equally, if not more important, for the purpose of doing what no other conservative or minimally invasive treatment

available today does; Which is to attempt to reverse the nerve damage to the trigeminal nerve, or at least slow its progress.

Dr Adahan was the world's first Medical Specialist to apply the Painshield to patients with problematic pain syndromes and has accumulated a broad experience in the application of this technology in neuropathic pain patients. Dr Adahan has been instrumental in developing the clinical indications, applications and usage protocols for the Painshield technology and is active in research and teaching in the field.

[Click here to see if you may be an appropriate candidate for this revolutionary and safe treatment approach.](#)

[Click here or more information on Dr Adahan](#)

[Want to know more about Ultrasound and it's role in treating Trigeminal Neuralgia? Click here](#)

[Click here for more information of trigeminal neuralgia and its treatments](#)



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To speak to Dr Adahan about a private consultation, simply submit this form:

Pour discuter avec Dr Adahan de la possibilité d'une consultation , veuillez remplir ce formulaire.

הז ספוט חלשו אלמ אנא , יטרפ קועי לבקל ידכ

Name / Nom / **מש**

Teudat Zehut / **ז.ת.**

Phone / NUMERO DE TEL. / **ל"ט רפסמ**

Alternate Phone / TEL. #2 / **דיינ**

Email / **לא"וד**

Describe the pain you wish to relieve:

Décrivez brièvement la douleur que vous souhaitez soulager:

: הב לפטל הצור התאש באכה תא ראתל הרצקב

If you consulted a doctor regarding your pain already, what were you told ?

Si vous avez déjà consulté au sujet de la cause de votre douleur, Quel a été son diagnostic?

הנחבאה התייה המ , מיבאכ לע אפור תרקיב רבכ מא?

To make the most of your visit with Dr Adahan- we suggest you [click here](#) to complete some forms that will help Dr

Adahan better understand your Pain

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The Pain Treatment Center

Dr. Haim Moshe Adahan, MD, LMCC



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המרכז
לטיפול ב...
לחץ כאן כדי לקבל ייעוץ



תילנימגירט היגלריונמ מילבוסל תעכ עצומ חוטבו ינשדח לופיט!
דנואסרטלוא תיגולונכט לע ססובמ אלא תוקירזב דורכ וניאו יחותני וא יתפורת וניא לופיטה
ינקירמאה תופורתהו קוזמל להנמ י'ע הנורחאל הרשוא רשא תידוהי

(FDA)

סינפב רתויב סיזע סיבאכ תמרזגה השק הלחמ איה, (תילנימגירט היגלריונ) שלושמה בצעה תנמסת.
רשמב תמצעתמו תכלוה סימוטפמיסה תעפוא רשאכ נמזה מע הרמחהל הייטנ שי הלחמל מילוחה בורב
השק המישמל רפוא מהב לופיטהש רכ סינשה

רא, סיכומנ סינונימב תונתינ רשאכ הלחמה לש סייתלחתה סיבלשב תוליעי ללכ קרדב תופורת סנמוא

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עודי רא מילוחה יב הבר הדימב הנתשמ תופורתה תוליעי. הנתקו תכלה נתעפשה מינשה תצורמב
נמזה סע מירבוגו מיכלוהה מיבאכהמ תקפסמ הלקה שיגרהל וקיסיפי מילוחהמ יצחכש

תודעוימ אלא הלחמה תומדקתה תא תוטאמ נניא שלושמה בצעה תנומסת ילוחל סויכ תונתינה תופורתה
תא פאו תופורתה וונימ תא ריבגהל נמזה סע מיצלנא מילוחה בור, נכ לע רתי. דבלב יטמוטפמיס לופיטל
יאוול תועפות לש תנכוסמ תורבטצהל סרוג רבדה. באכה תמר תא דירוהל ידכב תללוכה תופורתה תומכ
באכה תדרוהל תיחותינ היצפואב רוחבל מיצלנא מילוחהמ מיזוחא מישימח לעמ, רבד לש ופוסב. תונוש

תוחפ לדוגב הריעז העיגפ אוה הלחמב רושקה יארונה באכה רוקמש, עיתפמב הארה שדח יאופר רקחמ
תוברק מיתעל ריפה וניה רבודמ וילע יבצעה קזנהש הניה העיתפמ הדבוע דועו !מ"ס 0.5 -מ

יוצמה הזל המוד יבצעה קזנה רשאכ דנואסטרטוג תרזעב עוגפ בצע יופיר ודעית מייעדמ מירקחמ רפסמ
דלישנייפ"ה רישכמ לש תידוחיי היגולונכט. שלושמה בצעה תנומסת ילוחב" (PainShield)
העיגפה סוקמל תלוגלוגה קות לא יתוחיטב נפואב ילופיט דנואסטרטוג לש הרבעה הנושארל תרשפאמ
שלושמה בצעב

תועיבצמ דלישנייפב ולפוט רשא שלושמה בצעה תנומסת ילוח לצא תולבקתמה תומיהדמה תואצותה
הלא מילוחב, לכ תישאר. וז תנומסתב לופיטב דנואסטרטוג לש בושחה ודיקפת לע תיעמשמ דח הרוצב
בצעה תא אפרל יושע הז לופיט, רתוי בושח נכתייו פסונב. רתויב המישרמו הריהמ באכ תדרוה הגשוה
לגוסמ ינרדוח וניאש רחא לופיט מושש הרטמ גישהל רכבו קזנה תומדקתה תא טאהל תוחפל וא עוגפה
סויכ גישהל

סע מילוחב דלישנייפה תיגולונכט תא משיי רשא מלועב נושארה החמומה אפורה וניה נאהדא 'רד
יבצע רוקממ מינוש מיבאכ סע מילוחב וז היגולונכטב שומישב בר וויסינ רבצ רכו תויתיעב באכ תנומסת
ימוחתב ליעפ אוה נכ ומכו דלישנייפב מילופיטל מילוקוטורפו תויוותהה תמאתהל החמומו וניה נאהדא רד
TRIGEMINAL NEURALGIA המדריך השלם שלך ל

[ז חוטבו ינכפהמ לופיטל מיאתמ דמעומ התא פאה קודבל ידכ נאכ פחל](#)

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30/08/09 02:24 - ב מסרופ

30/08/09 15:52 - נורחא נוכדע

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ולשכנ מירחאש הפיא חילצה, לוק ילג תועצמאב באכב לופיטל "דלישנייפ"ה רישכמ

אריפש נר תאמ

מיכרדש תומוקמב עייסל חילצה, לוק ילג תועצמאב באכב לופיטל שדח ילארשי רזיבא *

ולשכנ תורחא

מינפב מיזע מיבאכל תמרוגה הלחמ איה, (Trigeminal Neuralgia) שלושמה בצעה תנומסת תוירעזמ תועיגפמ עבונ באכה, בורל. מינפב תושוחתל יארחאה ישארה בצעב תעגופ תנומסתה בצעב הגירח תושיגרל תמרוגה הצופנ תשרט ומכ, רחא רוקממ וא וילע עחולה נטק מד ילכמ בצעב רחאמ רא, מיבאכ רוכישל תופורת תרזעב אוה ולא מילוחב לבוקמה לופיטה. מדה ילכ מע עגמל תיצחמכ. ונימב הלדגה תשרדנו תתחופ תופורתה לש נתוליעי, הרימחמו תכלוהה הלחמב רבודמש באכה תא קתשל תנמ לע.... בצעה ברצנ ובש יחותינ קילה פוסבל מירבוע מילוחמה

TRIGEMINAL NEURALGIA ל קלש מלשה קירדמה

md,cm , LMCC,CCFP, FRCPc,FABPM+R, נאהדאהשמ -מייח ר"ד
. אביש מייח שש לע יאופרה זכרמב באכ מוקישל זכרמה שאר, Dip Sports Med

מיטרפ:

רמושה לת, אביש מייח שש לע יאופרה זכרמה

מזי זופשא

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מייחה תוכיאב רתויב מיעגופהו מירומחה מיבאכהמ דחא אוה Trigeminal Neuralgia-TN מ סרגנה באכה TN. מ מילבוס מילארשי מיחרזא 15000 "תודבאתה תלחמ " הנוכמ TN הקירמאב

בצעה תאיצי רחאל מ"ס 0.5 1st תשחרתמ העיגפה .מינפב השוחתה לע יארחאה בצעה לש הכיפהו הנטק העיגפ ללגב בורל תמרגנ TN תינמיה הנומתבש נבלמה קותבש רוזאב -חומהמ

באכה לש הליעיו הריהמ הלקה ווחי הלחמה לש ינושאהר בלשב מילפוטמה בור .הז רמסמב הנרקוסת נהו TN ב לופיט תוירשפא הברה שי המיאתמ הרוצב הלחמב ולפטי רשאכ תאז, הלחמה לש תונושאהר מינשב

מינופ מילוחמה יצחכו תוילאנויצנבנוק תויוברעתה תרזעב קר לופיטל רתוי השק היהנ בצמה, הלחמה תומדקתהו מינשה סע, רעצה הברמל לופיטב תוליעי תוחפ תויהל וכפה תופורתהש רכמ תעבונ וז הטלחה. חווט תכוראו הבוט רתוי האצות גישהל תנמ לע יגרוריקוריונ חותינ רובעל קורא חווטל תותיעב יאוול תועפותב הוול בורל יתפורתה לופיטה, פסונב. מהלש ונימה תא תולעהל קרוצ היהו באכב

TN מ מילבוסה מילוחל הווקת רתוי ותונ הז רקחמ. קרד קרופו מידקת רסח רקחמ קרענ אביש מש לע יאופרה זכרמבש ימוקישה זכרמב הלחמל סרוגה היעבה שרוש אוהש בצעל סרגנה קזנב לופיט י"ע תאז יאוול תועפות תוחפ סע באכב חווט תכורא הלקה גישהל האופרל 'גלוקהו ליגקמ תטיסרבינוא, דראוורה תטיסרבינואב מייאופר מירקחמ ודדוע תינשדחה היגולונכטהו וזה תינכפהמה תיאופרה השיגה TN. לל וורתפ ותיתש החוטבו השדח היגולונכט חתפל מתרטמש קרוי וינב תושעל TN ב הלוחה תא קזחל איה ותרטמש הזה הריקסה רמאמ לש אשונה מה תוילופיטה תויצפואה ראש לכ סע דחי וללה תושדחה תושיגה רתויב הבוטה הרוצב ובצמל עדומ היהיש רכל מורגלו ומצעל הנוכנה הריחבה תא

מ:יאשונ תמישר

ילנימגירטה בצעה לש ספת תנומסת לש מימרוגו מיניפאמ: וןשאר קלח
1. Trigeminal Neuralgia-TN (Tic Douloureux) לע תיללכ הריקס.
2. Trigemunal Nerve ילנימגירטה בצעה לש הימוטנא.
3. Trigeminal Neuralgia לש מיגוס.
א. תיללכ הגצה

ב. Typical Trigeminal Neuralgia - תיסופיט TN
ג. Atypical Trigeminal Neuralgia -תיסופיט אל TN
ד. TN Pre-Trigeminal Neuralgia - מדק
ה. Multiple Sclerosis-Related Trigeminal Neuralgia - Multiple sclerosis ל הרושקה TN
ו. Secondary or Tumor Related Trigeminal Neuralgia -'לודיגל רושקה TN' וא ינשמ TN
ז. Trigeminal Neuropathy or Post-Traumatic Trigeminal Neuralgia -תיתמוארט-טופ TN וא תילנימגירט היתפוריונ
ח. TN "Failed" Trigeminal Neuralgia "תלשכנ"
Trigeminal Neuralgia ב לופיט: ינש קלח

מילופיטה לש תיללכ הגצה.1

2. תופורת

א. תורכה

ב. Carbamazepine (Tegretol®)

ג. Phenytoin (Dilantin®)

ד. Baclophen (Lioresal®)

ה. Gabapentin (Neurontin®)

ו. Trileptal (Oxycarbazepine®)

ז. רועה לע תינוציח החירמל מירישכת תרזעב יטאפוריונ באכב לופיט :

3. חותינ

א. תיללכ הריקס

ב. Microvascular Decompression Surgery-MVD -ירלוקסו ורקים ץחל תתחפהל חותינ

ג. Rhizotomies) בצעה לש סרה/העיצפ לש תורודצורפ.

הגצה. 1

2. Rhizotomies לש מיגוס

א. Percutaneous Glycerol Rhizotomy- Rhizotomy י"ע קרזומש לורצילג

ב. Percutaneous Balloon Compression Rhizotomy- רועה ץרד וולב לש ץחל ידי לע סרה

ג. Radiofrequency Rhizotomy

ד. Stereotactic Radiosurgery (Gamma Knife)

ה. Peripheral Trigeminal Nerve Blocks, Sectioning and Avulsions . ירפירפה ילנימגירטה בצעל (Nerve Blocks) בצע ימסוח תמישו עוטיק, ךותיח

ו. Microsurgical Rhizotomy

Trigeminal Neuralgia-TN-ילנימגירטה בצעה לש ספת תנומסת לש מימרוגו מיניפאמ :ןושאר קלח

1. Trigeminal Neuralgia-TN (Tic Douloureux) לע תיללכ הריקס

דע תוינש המכ -רצק נמז קרשמב מיניפואמה מיבאכ לש מיימואתפ מיפקתהב תנייפואמ תנומסתה. רתויב תובואכה תנומסתה תחא איה TN לש דחא דצב קר שגרומ TNמ מרגנה באכה. מייילמשח מיקושל מימוד וא תוריקדכ מישגרומו מייביסנטניא, מירומח מיבאכה. תוקד יתש יוריג ידי לע ותוא ררועל ונתינש וא ינטנופס נפואב תורקל לוכי פקתה לכ. מינפה לש ונתחתה מג מיתיעלו יעצמאה, ווילעה קלחב שגרומו מינפה, הסיעל, הייטש, הליכא, רוביד, עגמ מה באכה תא ררועל מילוכיה מיחכש מירבד. באכהמ מיעפשומה מירוזאב ללכ ךרדב, וידע עגמ לש לק, ררועתהל באכל ומרגי אל ללכ ךרדב באכה ירוזא לש הציחל וא הטיבצ. קושינו תחלקמ, רעיש תשרבה, מייניש חוצחצ

לש מיפסונ מיפקתה ררועל אל תנמ לע מינפה לש העונת וא רובידמ ענמיו אופק ראשי דימת טעמכ לבוסה מדאה, TN לש פקתה נמזב מינפה תותוועתה לש מיימואתפה מיפקתההש מינעוט TN לש מימדוק מיעטומ מירואת. באכ לש תיווע תוועתהל תולולע מינפה. באכ ךא הניש תעב מישחרתמ מיפקתה תורידנ מיתיעל. neuralgia epileptiforme. וא tic douloureux העפותל וארק נכלו תויוצרפתה מה לש ינשה דצל מירבוע אל מלועל מיבאכה פקתה נמזב. תוויפיצפס תוחונתב תואצמה וא הביכש נמזב עגרהל וא רימחהל מילוכי מיפקתהה. תדרפנ הרוצב מישגרומ מיבאכה, מינפה לש מידדצה ינשב עיפומ באכה מהב מירידנ מירקמב. מינפה

נכמ רחאל. תופורת ידי לע לופיטל מישק דואמו רתוי תופוחד מיתיעל מיעיפומ מיפקתהה נהב הפרחה לש תופוקתב וייפואמ TN לש באכה הפרחהה תפוקת עיגת אמש דחפב מייח TNב מילוחה ולא תופוקתב מג ךא ללכ באכ ויא נהב העיגר לש תופוקת שי תכשמנ הלחמהש לככ, ךכ תובקעב. תורצקתמ העיגרה תופוקתו תורומח רתוי תופוחד רתוי תויהנ באכב הפרחהה תופוקת נמזה רבועש לככ

.יחותינ לופיטב וא רתוי תויביסרגא תופורתב ררוצה הלוע רכ

הפירח TN לש מירקמב .מיפקתהה יב באכמ מילבוס אל ("הימרוגו Trigeminal Neuralgia לש מיגוס " האר) תיסופיט TNמ מילבוסה הפרחה נמזב .מינידע 'מילולמינ' וא טבוצ באכ שלושמה בצעה ידי לע מיבבצועמה מירוזאב חתפתהל לולע הכורא הפוקת רבכ תכשמנש וא עובק טעמכ באכ שיגרמ הלוחהש דע רכ לכ ההובג תורידתב מילוע באכה יפקתה הרומח

מידחוימ מינחבמו מילאיסאפ-וינרקו מייגולוריונ מינחבמ .הנממ מילבוסה לש ויתורוצל באכה ירואית לע תססובמ תיסופיט TN לש הנחבאה מירע תויהל מיבייח מיינישב וא מינפב מיבאכמ מילבוסש מילוח מיאורה מייניש יאפורו מיאפור, נכל. תוילמרון תואצות מינתונ ללכ ררדב האר) הנחבאה תא ללכ ררדב ששאי יאופר לופיט לש ריהז בקעמ. TN לש תירשפאה הנחבאל (" תופורת "

לש תויוגש תונחבא תופוחד מיתיעל .תנחבואמ הלחמהש דע ליעי אל יאופר לופיטו לבס לש מינש מירבוע TNמ מילבוסה תובורק מיתיעל ווינ, מייניע תויעב לש מינוש מיגוס, ילזנארפא סוניסב מוהיז, ירלובידנמ-ופמטה קרפמב היעב, מייניש תולחמ לש מינוש מיגוס תוללוק הלחמה (העודי הביס אלל) יטפוידא מינפ באכ, מינפה ירירש לש מיבאכ, מינפה לש הנרגמ, ice pick-like גוסמ הנרגימ, תילרופמטה מצעה לש ילופיט, מייניש תוריקע ווגכ מיליעי אלו מייחרכה אל "מילופיט" רפסמ ורבע ונלש מילפוטמהש מילגמ ונא מויכ וליפא. תויוגולוכיספ תוערפהו מג עבונ TN נוחבאב ישוקה. תויטוקרנ וא תויטויביטנא תופורתו קורה תטולבל מילופיט, תויספויב, ילאזאנה סוניסה לש מיחותינ, שרוש תוחיכש שי TNלש רכמו תנומסתה יופירב תולבלובמה העיגר לש תוינטנופס תופוקתמ, מינחבאמ מייגולוידרו מיינדבעמ מינחבמב רוסחממ . תיסחי הרידנ

מירגובמ מיאליגב רשאכ, שיא 100,000 לכל TN לש מירקמ 5 מיפסונ הנש לכ. שיא 100,000ל מישנא 100-200 איה TN לש תוחיכשה מויכ מג רא 50 ל 60 יב אוה TN תוצרפתהל עצוממה ליגה. 70 לעמ מיאליגב שיא 100,000למישדח מירקמ 25 -מירקמ רתוי מעיפומ רתוי טעמכ מייוכיס שי מישנל. ("הימרוגו TN לש מיגוס " האר) TN לש רחא גוס וא תיסופיט TN מיחתפמ מידלי וליפאו מיריעצ מירגובמ לש מירידנ מירקמ שי. ('תילרטליב TN') מינפה לש ינשה דצב מג TN וחתפי תנומסתהמ מילבוסהמ 2%. מירבגל רשאמ TN חתפל מילופכ .החפשמב מישנא המכ לצא עיפומ TN מהב TNל תיתחפשמ היטנ

2. Trigemunal Nerve ילנימגירטה בצעה לש הימוטנא

שי . V ימור רופסימב נמוסמ בצעה. שארהו מינפה תא מיבבצעמה מילאינרק מיבצע תוגוז 12 רותמ ישימחה בצעה אוה ילנמגירטה בצעה תונותחתה מינפה תאו (maxillary V2) יחלה תא, (Ophthalmic V1) יעוה חצמה תא מיבבצעמה מיפנע השולש בצעל מירירשה לע טלושו הרטרפמטו באכ תשוחת, מינפה לע עגמ תשוחת ריבעמכ דקפתמ ילנימגירטה בצעה. (mandibular V3) תסלהו .מינפה ירירש ראש לכ לע טלושש (VII רפסמ ילאינרק בצע) מינפה בצעל ילנימגירטה בצעה יב לידבהל שי .הסיעלל מישמשמה

חומה עזגל רישממ ילנימגירטה בצעה שרוש משמ . Gasserion ganglion ארקנש רוזאב מישגפנ ילנימגירטה בצעה לש מיפנעה תשולש

אבוהש עדימ. trigeminal nerve nucleus מִיארקנה מִידחוימ מִינוריונ רבצל מִיעיגמ מִיילמשחה מִילגניסה חומה עזג רותב. סנופה רותל תעדומ הנומת תלבקתמ סקטרוק לרברסבו חמב. סקטרוק לרברסלו חומל רלשנ אוהש ינפל ש דבועמ ילנימגירטה בצעה תועצמאב .מִינפהמ השוחתל

מהימרוגו Trigeminal Neuralgia לש מיגוס.3

תיללכ הגצה. א.

ל-רושקש Multiplesclerosis , TN-pre-TN , מִדק, TN-atypical-תיסופיט אל TN , TN-typical-תיסופיט TN : TN לש תורוצ 7 מִירידגמ ונחנא TN multiple-sclerosis-related TN, תוכירצ TN לש ולא תורוצ. failed TN-לשכנ' tTN (Trigeminal neuropathy מִג ארקנ)יתמוארט טסופ TN, secondary TN-ינשמ TN ילאיסאפ וינרק באכל תומרוגה תורחא תונמסתמו idiopathic (atypical) facial pain תולדבנ תויהל

ב. Typical Trigeminal Neuralgia - תיסופיט TN. (Tic Douloureux מִג תארקנ)

TN לש מִירקמה לכ טעמכ. "Classical, Idiopathic and Essential TN: משה תא הלבִיק הנורחאלש TN לש רתויב הצופנה הרוצה יהוז לע ירלוקסו -ורקימה וא ירלוקסו-וריונה ןחלה. חומה עזגל ותסינכב ילנימגירטה בצעה שרוש לע מִד ילכ לש ןחל תובקעב מִמרנג תיסופיט אלש מִישנא לצא. ילנימגירטה בצעה מע עגמ מהל שיש מִינסק וא מִילודג מִידירו וא מִיקרוע ידי לע מִרגהל לוכי ילנימגירטה בצעה שרוש ילנימגירטה בצעה מע מִד ילכ לש עגמ ןיא ללכ ךרדב TNמ מִילבוס

ילנימגירטה בצעה לע מִד ילכ לש ןחל ןיא ללכ ךרדב TNמ מִילבוס אלש מִישנא לצא.

ילנימגירטה בצעה שרוש לע ירלוקסו ןחל שי תיסופיט TNמ מִילבוסה בור לצא

לולע הז, בצעה לע מִיסלופ לש רזוח יוריג שי רשאכ ךא בצעה לש קזנל דימ מִימרוג אל ילנימגירטה בצעה שרוש לע מִדה ילכ לש מִיסלופ איבמ רבדהש הארנכ, נמזה מע. ילנימגירטה בצעה לשnucleus)) ןיערגל מִיילאמרון אל תותוא תחילשלו בצעה דוקפתב מִיונישל מִורגל TN.ב שגרומש באכה תא רצוי הזו ילנימגירטה בצעה ןיערג לש רתי תוליעפל

מִירחא מִידירוו מִיקרוע מִג ךא, ילנימגירטה בצעה לע ירלוקסו-וריונה ןחלה לע יארחא בורלש מִדה ילכ אוה superior cerebellar ה קרוע חותינ. ילנימגירטה בצעה שרושמ ירלוקסו-וריונה ןחלה תא ליעי נפואב ררחשמ חותינ ידי לע אפרתהל לוכי TN. ךכ לע מִיירחא תויהל מִילוכי Trigeminal Neuralgia' לש לופיט': ינשה קלחב ראותמ אוהו microvascular decompression-MVD ארקנ הז

ג. TN -Atypical Trigeminal Neuralgia-תיסופיט אל

תיסופיט TN מב מישגרום אלש באכ יגוס-- הפירש וא תוחידק ויעמ, תוטיבצ תשגרה לש רומחו עובק ידדצ דח באכב תנייפואמ תיסופיט אל TN ילנימגירטה בצעה ידי לע מיבבצועמה מינפב תומוקמב מילק הפירשו תוטיבצ לש באכ הב חתפתמש תיסופיט TN תל תיסופיט אל TN ויב לידבהל שי

אל TN ש מינימאמ מנשי. תיסופיט אל TN לש מירקמ הברהל מרוגה מג תויהל בשחנ, תיסופיט TN ובנראית רבכש יפכ, ירלוקסו חל TN ש תונעוט תורחא תוירואת, (portio minor ארקנה) ילנימגירטה בצעה לש מיוסמ קלח לע מד ילכ לש חל תובקעב תמרגנ תיסופיט הלש תוחתפתה וא תיסופיט TN לש רתוי הרומח הרוצ איה תיסופיט אל

תמגודל, תיסופיט TN תושמשמה תופורת ידי לע, יקלח נפואב תוחפל, לקומ תויהל לוכי תיסופיט אל TN לש באכ תיסופיט TN ילוח יופירל ומכ הדימ התואב אל רא תיסופיט אל TN ילוח הברה יופירל לעי MVD חותני. carbamazepine (Tegretol®) רוביסל מורגת איהש מיוכיס רתוי שי רא תיסופיט אל TN לופיטב תיביטקפא תויהל הלוכי (בצעה סרה) rhizotomy לש הרודצורפש נייצל בושח מינפה לש תובאוכ פאו תוקיצמ (מילולמינ) תויומדרה לש

ד. TN Pre-Trigeminal Neuralgia -מדק

ידי לע מיבבצועמה מינפב תומוקמב תורזומ תושוחת מיווח מילוחמה קלח, TN לש באכ לש נושארה פקתהה ינפל מינש דע מימ TN מיעפשומו תויהל מידעומה תומוקמ, ילנימגירטה בצעה מדק TN. מדק לש מימוטפמס תויהל תולוכי (תויזטסאראפ, מיטחמו תוכיס ומכ) תוחונ יא וא (מייניש יבאכ ומכ) באכ לש ולא תורזומ תושוחת ותוא לידבהל נתינ, עיפומ TN לש נושארה פקתההשכ. תיסופיט TN לופיטל דעוימה יאופר לופיט ידי לע רתויב הליעיה הרוצב לפוטמ TN. TN מדקמ רורב

ה. TN Multiple Sclerosis-Related Trigeminal Neuralgia -Multiple sclerosis ל הרושקש

תלחמל תויאר שי TN מב מילוחמה 2%-4% ל. תיסופיט TN לש מימוטפמיסל מיהז multiple sclerosis (MS)-related TN לש מימוטפמיסה לש נושארה פקתהה תא מיווח מה רשאכ מיריעצ ללכ ררדב MS תל הרושקה TN ב מילוחה. TN מיחתפמ MS מב מילוחמה 1% ררעבו MS . MS מב מילוחה ברקב רתוי צופן (ילרטליב) ידדצ וד TN, פסונב. תיסופיט TN מב מילוחה רשאמ רתוי הרצק הפוקת קשמב חתפתמ באכה באכה MS. TN חתפתהל לולע, ילנימגירטה בצעה לש תכרעמה תא מיללוק ולא מירוזא רשאכ. חומב וילאימ יעוגפ מירוזא תורצווהל מרוג MS תועצבתמ (בצעה לש סרה) Trigeminal rhizotomies. ('תופורת' האר). תיסופיט TN תל תודעוימה תופורת ותוא מע לפוטמ TN רושקה שרוש לע ירלוקסו-וריון חל אוה רכל רידנה מרוגה TN מע MS מילבוסה מדיחי המכ רובע. באכה לע הטילשב תוליעי אל תופורתה רשאכ MDS- microvascular לש חותני עצבל ולקשי ולא מירקמב. CT וא דחוימ MRI ידי לע תאז תוהזל רשפאו ילנימגירטה בצעה TN. רושקה MS מב לפטל תנמ לע decompression surgery

ו. TN Secondary or Tumor Related Trigeminal Neuralgia -לודיגל רושקש TN' וא ינשמ

מילולמינל מורגל לוכי ילנימגירטה בצעב רומח נפואב עגופ וא חולש לודיג. ינשמ TN ארקנ לודיג נוגכ, רחא עגפ ללגב מרגנש TN לש באכ ('Trigeminal Neuropathy or Post-Traumatic Trigeminal Neuralgia' מג האר) טבוצ באכל וא/ו הסיעלה ייריש לש השלוחל, מינפב העיגרמ ללכ ררדב לודיגה לש חותינב הרסה. הנושארה מעפב מתחיקלב וליפא ינשמ TN מ מרגנה באכ לע טולשל תורזוע ללכ ררדב תופורת, ילנימגירטה בצעה לע דירו וא קרוע לש חל מג אוצמל מילולע, לודיגה תאצוה רחאל, חותינה נמזב. רזוח בצעה לש דוקפתה באכה תא משב הקינכט ידי לע קחרומ תויהל בייח חוליה מדה ילכ, TN תא אפרל תנמ לע, הז הרקמב. TN לש מינייפאמל מרוגה חל microvascular decompression.

Trigeminal Neuropathy or Post-Traumatic Trigeminal Neuralgia -תיתמוארט-טסופ TN וא תילנימגירט היתפוריונ ז. חתפתהל הלוכי תיתמוארט טסופ TN וא תילנימגירט היתפוריונ .רומח באכ לש הז בצמל סורגל תולוכי ילנימגירטה בצעה לש תועיצפ (Caldwell Luc תורודצורפ תובקעב ומכ)סיסוניסב המוארט, פיינישב המוארט, (פיכרד תנואתב ומכ) תילאיסאפ-ינירק המוארט תובקעב TN. לב לופיטל תושמשמה (rhizotomies)תוינסרה תורודצורפ תובקעב רקיעב לבא phantom pain פיתיעל ארקנש באכו תומוד תודירטמ תושוחת מע דחי (פילולמינ)תויומדרה עיפוהל פילוכי ילנימגירטה בצעה לש העיצפ רחאל. הז בצע לש(nucleus) ויערגה לש תינשמ תוליעפ רתיו ילנימגירטה בצעל ריפה יתלב קזנ ללגב סימרגנ ולא סיבאכ. deafferentation pain

ידי לע רמחומ תויהל לוכיו רעוב וא טבוצ באכה. עובק באכ ללכ כרדב אוה תיתמוארט טסופ TN וא תילנימגירט היתפוריונ לש באכה, הלחמה לש תינוציק יכה הרוצב. בצעה תעיצפ רחאל סינש דע סימי וא תידימ ליחתהל לוכי הז באכ. רוקו חור ומכ סיררועמ סירגירטל הפישח, טלחומ לולמינ שי סהב סירוזאב קשמתמ רומח באכ שי, anesthesia dolorosa ארקנה בצמ.

סירואית מנשי. תופורת ידי לע טלשנ יתלב תויהל לולע באכהו ליעי אל תובורק פיתיעל אוה תיתמוארט טסופ TN לש לופיט, רעצה הברמל תויןרדוח תורודצורפ דוע מנשי. (trigeminal nerve stimulation) 'ילנימגירטה בצעה יוריג לש הרודצורפ תובקעב תמרגנה באכב הלקה לש /tractotomy)חומה עזגב תודקוממ תועיצפ וא pre-motor cortex ה לש יוריג ומכ -נתוסנל נתינש

n. TN "Failed" Trigeminal Neuralgia "תלשכנ"

סא. תיחותינ תוברעתה פילקוש, רתיו תורזוע אל תופורת רשאכ. תיחותינ תוברעתה וא תופורת ידי לע TN לש סירקמה לכב טולשל נתינ אל וא רזוח חותינ עצבל כרוצ שי תורידנ פיתיעל. רתיו הליעי הרוצב דובעל תולוכי נה זאו תופורת בוש פיסנמ,חותינ רחאל קשמנ וא רזוח באכ ארקנ הז בצמ. באכה לע הטילשב תוליעי אל תואצמנ תויחותינה תורודצורפהו תופורתה לכ פילוח לש דואמ הנטק הצובקב, רעצה הברמל. פסונ תוינסרה תויוברעתה תובקעב תיתמוארט טסופ TN וא תילנימגירט היתפוריונמ סג פילבוס תובורק פיתיעל פילוח ולאכ. "תלשכנ" TN עזגב תרקובמ העיגפ, pre-motor cortex ה לש (stimulation יוריג ומכ סירקחנ ויידעש פילופיט עצבל לוקשל פילוכי ולא סירקמב. ורבעש Gasserion ganglion ה לש וא ילנימגירטה בצעה לש יוריג וא (tractotomy) חומה

Trigeminal Neuralgia לש לופיט :ינש קלח

מילופיטה לש תיללכ הגצה.1

.נאכ וגצוי מלוכו TNב תוילופיט תושיג לש פייסיסב פיגוס העברא שי

1. .בצעבש קזנב לפטלו הווקת תתל תולוכיש יאוול תועפות אללו תויביטברסנוק, תויתפורת אל תושיג.
 2. .חומה לע תועיפשמה תויתכרעמ יאוול תועפות אלל ביאכמה בצעב מילפטמה פינפה רוע לע תינוציח החירמל מירישכת
 3. .מירחא מירביאב וא חומב יאוול תועפותל סג מורגל מילוכיה מירודכ
 4. (Rhizotomy) באכב הלקה גישהל תנמ לע קזנל טעמ קיזהל נתרטמש תורודצורפ
 - א. .היעבה מוקממ מ"ס המכ קזנ תמירגו בצעל טחמ תסנכה תושרודש תורודצורפ
 - ב. .היעבה מוקמב שממ לפטמו בצעל טחמ תסנכה שרוד אל Stereotactic Radiosurgery (Gamma Knife)
 5. .נוכיסה תא הכותב תללזכ קא רורא חווטל באכב הלקה לש רתויב הובגה רועישה סע הקינכטה איה חומ חותינ -תיחותינ תוברעתה
- .עובק יגולוריונ קזנ לש רוביסל יתועמשמה קא רומנה

1. .הלחמה בצק תא טאהלו בצעבש קזנב לפטלו הווקת תתל תולוכיש תוחוטבו תויביטברסנוק, תויתפורת אל תוילארשי תושיג

לעב דנואס ארטלוא .באכב הלקה עוגפ בצע שודיח לש לאיצנטופ מירקחמ המכב הארה מיכומנ תורידתו המצוע לעב דנואס ארטלוא מיטסיפרתויזיפו מיאפור מהב ושמשתשהש שנואסארטלואה ירישכמל האוושהל ותינ אל וליפאו הנוש דואמ אוה מיכומנ תורידתו המצוע מייטסוקא מילג לש תוילקיזיפה תולוגסב שמתשמש מלועב נושארה אוה, השדח תילארשי היגולונכטב תושמתשהב , נאהדא ר"ד .רבעב לארשיב ילנימגירטה בצעה לש עוצפה קלחל מיכומנ תורידתו המצוע לעב דנואס ארטלוא חולשל תנמ לע surface acoustic waves -חטשה ינפ לע TN. לש בצמב

לש תוליעי לע וחווידש הלחמה לש מדקתמה בלשב מילוח לש מירקמ 30 ברקב החלצה 80% נאהדאר"דל התייה וז הטישב שומישב ,ינקירמאה תופורתוהו נוזמה להנמ לש ימז רושיא הל שיש וזה היגולונכטה סע נאהדאר"ד לש ררדה תצרופ תינילקה הדובעה .לופיטה היגרוריוכוריונה הקלחמה סע הלועפ פותישבו מוקישו תילקיזיפ האופרל ילארשיה דוגיאה לש הרכהב ותוא התכיז , יפוריאה דוחיאה קרוי-וינב האופרל גלוקה לש באכ מוקישל הקלחמהו לוארטינומב יגרוריוכוריונה נוכמה לש רקחמה תקלחמ שאר, דרווראה תטיסרבינוא לש

-תורחא תומייק תוטיש ינפ לע וזה הריעסמהו השדחה תילופיטה השיגה לש מילודגה תונורתיה

1. ללכ מירודכב שומיש אלל באכה תדרוהל מורגל הלוכי פא, נמזה מעו תופורת ינונימב התחפה תרשפאמ הטישה
2. TN.ב לופיטל מיחקלנש מירודכהמ קלח ומכ אלש -תומצעה חמ וא תומצעה, דבכה, חומה לע תועודי תויתכרעמ יאוול תועפות ניא
3. Rhizotomy ה תורודצורפ ומכ מיבצעה תכרעמ לש סרה/העיגפ תברעמ אל הטישה
4. תא מקשל הכומנ המצוע לעב דנואס ארטלואה לש לאיצנטופה ררד תאזו ואצומב בצעה לש יופיר תרשפאמ מצעב הטישה (וז. תילופיט השיג לע מויכ רקחמה לש אשונה וזה) תיבצעה תכרעמה
5. תנכוסמ הנרקל הפישח תברעמ אל הטישה
6. נכוסמ חומ חותינ תברעמ אל הטישה

2. חומה לע תועיפשמה תויתכרעמ יאוול תועפות אלל ביאכמה בצעב מילפטמה מינפה רוע לע תינוציח החירמל מירישכת

נויבס תעבג מראפ-רפוס להנמו יארחא חקור רוצ לויא מ חוקל אבה טסקטה
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: רועה לע תינוציח החירמל מירישכת תרזעב יטאפוריונ באכב לופיט

באכ רכשל וחילצישו רועה לע מתוא משייל נתינש מידחוימ מירישכת חתפל הז תופורתה תיישעת ינפב מידמועה מילודגה מירגתאה דחא תועפות לפוטמהמ רוסחי רועה ררד הפורת לש ימוקמ נתמש הדבועב הצוענ רכל הביסה. טרפב TN ומכ ינורכ יטאפוריונ באכו ללכב . דבכב קורפי תורבועו הפה ררד תוחקלנה תופורתל תונייפואה יאוול זוכיר- רועה לש תונילעה תובכשב שרדנה רוזאב ולש מיהובג מיזוכירל עיגהל נתינ רועה ררד ליעפה רמוחה לש זכורמ נתמ 'יע פסונב (1). ליעפה רמוחה לש יאוולה תועפות תולבגמ בקע (הפה ררד) ילרוא נתמב וילא עיגהל דואמ השקתנש ענמיהל זכ הרוצבו ילרואה ונימב תדרל נמז ררואל היהי נתינ יטראוית פואב, תינוציח החירמו ילרוא נתמ תבלשמ לופיטה תינכותו הדימב . יאוול תועפותמ רתוי . (רועה ררד) ילמרדסנרט נתמ יבל ילקיפוט-ינוציח נתמ יב לדבהב יחבהל יואר עיגמ אלו רועה לש תונילעה תובכשב עיפשם נושארה דועב רועה ררד הפורת נתמ 'יע תימטסיס העפשהל איבהל ותרטמ נורחאה . תימטסיסה תכרעמל . אצמנ עוגפה בצעה מא קר החלצה ייוכיס שי ילקיפוט לופיטלש חניהל ינויגה, ינורכ יטאפוריונ באכ לע מירבדמ ונא רשאכ יטראוית נפואב . רועה לש תונילעה תובכשה רוזאב . ניטולחל ילאיבירט ונניא רועה ררד תופורת רידחהל רגתאה . מייוצר אל מירז מירמוח תרידחמ ונפוג לע נגמה רתויב ליעי מוסחמ הוואמה (SC) Stratum Corneum -ה תבכש איה ירקיעה מוסחמה (2) :מיללכ רפסמ מנשי וז הבכש רודחלו תוסגל תנמ לע רתוי לק היהי רכ רתוי יליפופיל ליעפה רמוחהש לככ(1) . הטמו רטמ ונ 36 -ה רוזאב תויהל בייח מיקיקלחה לדוג רמולכ, רודחל תנמ לע ירלוקלומ בצמב תויהל בייח ליעפה רמוחה(2) . רתוי לודג רודחיש יוכיסה רכ הטמו נוטלד 600 תוחפלו רתוי נטק ליעפה רמוחה לש ירלוקלומה לקשמהש לככ(3) . רודחל וייכיס ורבגי רכ ננוימ תוחפ היהי ליעפה רמוחהש לככ(4) . SC-ל היצלופינמל מימרוגו הרידח מיציאמה מידחוימ מירמוח רועה לע משיימה ליעפה רמוחה לש אשנב בלשל ררוצ שי(5) . יטאפוריונ באכב ליעי לופיטל שמשל תולוכיש תוילקיפוט תופורת מלועב מויה תומייק אלו טעמכ EMLA, לארשיב תומושר אלש 5% זוכירב ניאקודילה תוקבדמ נה מלועב שומישב מיאצמנו וקדבנש מידחיה מירחסמה מירישכטה לש תיטקטואא תבורעת

Prilocaine 2.5%+ Lidocaine 2.5% Capsaicin (Zostrix) תחשמו סרקב .

. תלבגומ דואמ ינורכ יטאפוריונ באכ לע ולא מירישכת תשולש לש העפשהה

תחיקרב מיחמומה תחקרמ יתבב תוחקרנה תופורת תרזעב תישענ הז יפיצפס מוחתב סויה תעצבתמה תיתועמשמה תוליעפה בור . ולא מידחוימ מירישכת

PLO : ארקנ רועה ךרד מיליעפ מירמוח תלבוהל שמשמה ירקיעה אשנה

Pluronic Lecithin Organogel .

. תוזאפה יתש לש סייפרטניאב תובשויה תולצימ לש תכרעמו תינמוש הזאפ, תימימ הזאפמ בכרומה לגב רבודמ

יטיצל ליכמה ביצי מוידמ אוה PLO. ב'הראב דחוימבו מלועה לכב רועה ךרד באכב לופיטה מוחתב דואמ בחרנ שומישב אצמן הז לג

. SC -ה ךרד מיליעפה מירמוחה תרדחהל מירזוע מו ותוא מיבצימ מגש מדיפילופסופל רוקמכ

: ינורכ יטאפוריונ באכב לופיטל ירוע ותמב מישמתשמש מיליעפ מירמוחל תואמגוד

Ketamine, Lidocaine, Gabapentine, Carbamazepin, Clonidine, Methadone,

Ketoprofen, Amitriptyline, Dextromethorpan דועו.....

מע בולישב וא דבל Ketamine -ב שומיש לע תנוש תודובע ומסרפתה הנורחל

(3). מיינורכ מייטאפוריונ מיבאכב לופיטל PLO -ב Amitriptyline

Allodynia תדרוהל Ketamine 10% In PLO לש תוליעי הקדב תודובעה תחא

. (4) ובצלפ תמועל תיטסיטטס קהבומ נפואב ליעי ותוא האצמו CRPS מע מילפוטמב

. Case Studies -ו תוטודקנא לע ססובמ עדימה בורו דואמ הנטק הז מוחתב ועצובש תורקובמה תודובעה תומכ

ילקיפוטה אשנה רותימ תולוקלומה תרידח ץיאהל תנמ לע Phonophoresis -ה תייגולונכטב שומישה אוה הז מוחתב מייקה ףסונ רגתא

(5). עוגפה בצעה רוזאל רתוי הבר תוליעיבו תולקב עיגהל רוזעל נכתיו רועה לש תוקומעה תובכשל רועה לע משוימה

תורידתב דנואסרטלוא ילגב תשמתשמה היגולונכט איה Phonophoresis

. SC -ה ךרד תולוקלומ תרידח ץיאהל תנמ לע 0.75-3.0 MHz

. SC-ה תא רודחל תולגוסמה תולוקלומה חווט תא ביחרהל הלוכי וז היגולונכט

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מילופיטה לש תיללכ הגצה.1

carbamazepine (Tegretol®), phenytoin (Dilantin®), gabapentin (Neurontin®) תוללוק ןהו TNב נושארה לופיטה ןה תופורת

לוכיש רבד -תופורתה לש ןונימה תאלעהב ךרוצ שי, רתוי באוכו רידת היהנ באכהו תמדקתמ הלחמהש לככ. baclophen (Lioresal)® ו

רבד לש פוסב רא ל"נה באכלו תופורתל הנוש לבס ףס שי הלוח לכל. מיבאכה לע הטילשב יוקילב וא/ו תולבסנ יתלב יאוול תועפותל ליבוהל

לש חותינ עזבל ולקשי הז בלשב .םהלש הלחמה תומדקתהל קפסמ נפואב תורזוע אל תופורתהש ולגי סילוחמה יצח תוחפל
rhizotomies – או microvascular decompression surgery העיגפ לש הרודצורפ .

2. תופורת

א. תורכה

ןיידע רא) רתוי המלש הנומת לבקל תנמ לע תפרוצמה הלבטב ןייעל ןתינ . TNב לופיטל רתויב תוצופנה תופורתה ןה הטמל תונודנה תופורתה
TNב לופיטל תופורת לש (ןיטולחל המלש אל

-ןאהדאהשמ -םייח ר"ד ומכ בחרנ ןויסנ לעב באכב החמומ םע השיגפ מאתל ץלמומ ,רתויב רבצמל המיאתמה הפורתה תא רוחבל תנמ לע

md,cm , LMCC,CCFP, FRCPc,FABPM+R,

םיטרפ . אביש פייח םש לע יאופרה זכרמב באכ מוקישל זכרמה שאר , Dip Sports Med

רמושה לת ,אביש פייח םש לע יאופרה זכרמה

םוי זופשא

'םייחל'ןיינב

19 רפסמ דרשמ

םוקישה זכרמ

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carbamazepine תוללוכו (מיסוכריפ תודגונ) anti-convulsants תוארקנש תופורת תועצמאב תלפוטמ ללכ ךרדב TN, מויכ רוביצל הגצוה Phenytoin . Phenytoin (Dilantin®), oxycarbazepine (Trileptal®) ן gabapentin (Neurontin®) (Tegretol®), phenytoin תוליעיל ףיסוהל הלוכי Baclophen (Lioresal®). רתויב הצופנה הפורתה תויהל הכפה carbamazepine 1962בו 1942 תנשב הנושארל הרקי איהש ףא לע תאזו יאוול תועפות תוחפ הל שיש ללגב בחר שומישב התייה (gabapentin), Neurontin®, ולא תופורת לש לש רתיה תוליעפב התחפה ידי לע TNה יפקתה תא תיחפהל תורומא וללה תופורתה .Tegretol®מ הליעי תוחפ תמייסומ הדימבו חומה עזגבש nucleus.

ףא מא .לבסה חוכו ךרוצה יפל הפורתה ןונימ תא מילידגמ . Neurontin® וא Tegretol® לשמל תחא הפורת מע ליחתמ ללכ ךרדב לופיט בור לצא ליעי אצמנ יאופר לופיט הלחמה תליחתב .תופורת דוע מע בולישב וא דבל תורחא תופורת מיסנמ, הליעי תאצמנ אל הפורת תועפות ללגב וא באכה לע הטילשב קיפסמ ליעי אל אוהש ללגב יאופרה לופיטהמ מיצורמ אל ףוסבל TN ילוחמ יצחכ, רעצה תיברמל .מילוחה .מילקשנ מייחותינ מילופיט הז בצמב .יטיב ידיל תואב דימת טעמכש תופורתה לש יאוול

ב. Carbamazepine (Tegretol®)

1-)רומנ אוה הפורתה לש יתלחתהה ןונימה . carbamazepine -ה תרזעב באכב תיתועמשמ התחפה מיווח תיסופיט TNמ מילבוסה לכ טעמכ ןונימ תחיקלב עיפוהל הלוכי באכב תיתועמשמ הלקה . יאוול תועפות תועיפומש וא ןיטולחל רבוע באכהש דע הגרדהב הלועו (מויב תולולג 2 ןונימ שרדנ מירומח מפקתה נמזב .מויל תולולג 4-3ל מיקלוחמש ג"מ 1600 ל 600 ןיב ענ ללכ ךרדב עיפשמש ןונימה לבא הפורתה לש רומנ הגופה לש תופוקתב .ןונימה תא מידירומש דע מיעובש ךשמב תוחפל ןונימ ותוא תחקל מיכישממ תגשומ באכב הלקהש עגרב .רתוי הובג .הגרדהב הפורתה ןונימ תא דירוהל ןתינ

היסקטא , (מייניעה לש דוציר תועונת)סומגטסינ ,תרוחרחס , ישפנ לובלב ,סונמינ ןה תולוכי ןונימל מאתהב תועיפומה יאוול תועפות רפסמ

תא דירוהל נתינ תורומח נה יאוולה תועפות מא .(נובאת לש נדבוא)היסקרונאו תוליהב, (הלופכ הייאר)היפולפיד, (היצנידרואוקב הדירי)
ונוימה תא בוש מילעמש ינפל מימי 3-1 carbamazepine לש ימויה ונוימה
עיפוהל הלוכיש רועה לש תיגרלא החירפ איה לשמל תאזכ הבוגת .ונוימל תורושק אלש carbamazepine ל תויניצר קא תורידנ תובוגת מג שי
הפורתה תליטנ תליחת רחאל אוהש יתמ
מדה יאת תומכב הליפנ)סיזוטיצולונרגא וא הינפוקול תללוכה מדה תכרעמב הערפה מיחתפמ carbamazepine מילטונש מילוחמה 6%-2
(הריצא)מימ תלערה, דבכ תלערה: מירחא מירידנ מיכוביס מג מנשי .(מד יאת רצייל קיספמ מצעה חומ רשאכ)תיטסלפא הימנא וא (מינבלה
מעטה שוחב תוערפהו תוילאוזיו תויצניצולה , (congestive heart failure)תיבבל היעב, (מדב מידוס לש הכומנ תומכ) הימרתנופיה, (מימ לש
ינימה דוקפתב וא
תליטנ תא קיספהל שי .מעפ ידמ מד תוקידב תוחקלנ הב שומישה רחאלו הפורתב שומישה ינפל מד תקידב תחקלנ ולא מיכוביס תובקעב
תובוגתהמ תחא העיפומ מא דימ אפורל אורקלו מד תוקידב עצבל שי .ילאמרונהמ הכומנ תייהנ תונבלה מדה תוירודכ תריפס מא הפורתה
(רועה יבג לע מינטק מימתכ) petechiae וא הלק הלבח, (הפה ללח לש באוכ מוהיז) stomatitis , נורג באכ, מוח: תואבה

מינונימב חקלהל תבייח קא הלערהל מינוכיסו יאוול תועפות תוחפל מורגל הלוכיש Tegretol® לש השדח הרוצ איה Oxycarbamazepine
באכה לע הטיילשה תמרב תוותשהל תנמ לע רתוי מיהבג.

ג. Trileptal (Oxycarbazepine)

הפורתש אצמנ הנורחאל .מיבצמ לש ונוגמל מיאפור ידי לע רתויו רתוי תמשרנש Tegretol® לש הרוצ איה oxycarbamazepine או Trileptal
תורידתו תורומח תוחפ הלש יאוולה תועפות לבא מיסוכרפ תדגונ הפורת וז , Tegretol® ומכ . TN ב מילוח המכל הליעי וז
ג"מ 2400-3000 אוה ילמיסקמה ונוימה .באכה לע הטיילש גישהל תנמ לע הגרדהב הלועו מויב מיימעפ ג"מ 300מ ליחתמ ללכ כרדב ונוימה
המישנה תכרעמב מוהיז, החירפ נה תוצופנ תוחפ נהש תועפות .דערו תופייע, תרוחרחס, תואקה, תוליהב נה תוצופנ יאוול תועפות .מויל
Trileptal תחקל תוסנל ול רוסא (carbamazepine) Tegretol® ל תיגרלא הבוגת הווח הלוח מא .מדב מיטילורטקלאב מיינוישו הלופכ היאר
הגרדהב תושעהל מיכירצ ונוימה לש הדרוהו האלעה סוכרפ תודגונה תופורתה ראשב ומכ

ד. Phenytoin (Dilantin®)

יצח לעמ לצא (תינוצר יתלב מירירש תוצווכתה) 'מיקיט' גוסמ מיבאכ לע לקמ מויב מימעפ 3-ל קלוחמה ג"מ 300-500 לש ונוימב Phenytoin
לש הרמוחב יולת ילמיסקמה ונוימה . TN לש הרומח הפרחה לש בצמב ידירו רות נפואב ונתהל מג הלוכיח Phenytoin ה תפורת . TN ילוחמ
היסקטא, (מייניעה לש דוציר תועונת)סומגטסינ תוללוכ (ונוימב תויולתה) יאוולה תועפות .הפורתה תחקיל מע תוררועתמש יאוולה תועפות
תופסונ תועפשה .ישפנ לובלבו מונמינ , (ניעה תועונת לש קותיש) היגלפומלתפוא , (רובידב ישוק)הירטראסיד, (היצנידרואוקב הדירי)
מג עיפוהל מילולע . (תפדוע רעיש תחימצ)סיזוכיטרפיה , (הפה תושימגב הילע)מייכניחה לש היסלפרפיה לולכל תולולע הפורתה לש
מדה תכרעמב תוערפה וא דבכה לש קזנ, רועב תיגרלא החירפ ומכ מירומח קא מירידנ מיכוביס
ה.

Baclophen (Lioresal®)

בולישוב הב שמתשהל נתינ לבא , TN רובע phenytoin או carbamazepine לש תוליעיה תמרל המוד הניא Baclophen לש תוליעיה תמר
ונוימה .תויתגרדהב תולעל לוכי אוה מויב מימעפ 2-3, ג"מ 5 ללכ כרדב אוה Baclophen לש יתלחתה ונוימה .ל"נה תופורתהמ תחא מע
וצלאי Baclophen מילטונה מילוחש כח חווט תרצק העפשה שי Baclophen ל .מויל ג"מ 50 ל 60 יב ענ באכה תא ריבעהל תנמ לע חקלנש

תועש 3-4 לכ פסונ ונימ תחקל

לע תתחפומ ולא יאוול תועפות לש תועראהה .מייגרב השלוחו תוליחב ,תרוחרחס ,תופייע תוללוק Baclophen לש תוירקיעה יאוולה תועפות . baclophen ה תליטנ תא לובסל מילוכי אל מילוחמה תירישעל בורק .הגרדהב ונימה תאלעהו Baclophen לש רומנ ונימב הלחתה ידי קיספהל יא .הפורתה תליטנ תקספה מע דימ מייטסמ הז בצמ רא baclophen ה תליטנ רחאל רצק נמז עיפומש לובלב בצמ אוה רידנ רוביס נורחאה ונימה ,ולא מימוטפמיס מיעיפומ מא.מיפקתהו תויזה ועיפוי נפ הב שומיש לש הכורא הפוקת רחאל תחא תבב הפורתה תליטנ תא .הגרדהב תחפומו שדחמ משרנ ,קדבנ הפורתה לש

1. Gabapentin (Neurontin®)

carbamazepine ומכ טעמכ הליעי וז הפורת . GABA רטימסנרטוריונל ינבמ נפואב הרושקש טיטפליפא יטנא הפורת איהGabapentin יאוולה תועפות .ילמיסקמ ונימל דע הלוע הז ונימו מויב מימעפ 3 ג"מ 300 ללכ ררדב אוה יתלחתה ונימה . יאוול תועפות תוחפ הל שי Tegretol® תופורתה תא דחיב לוטל נתינ.(מייניעה תועונת דוציר)סומגטסינו השלוח , (היצנידראוקב הדירי)היסקטא , תוינונשי תוללוק תוצופנה תושק תובוגת הנעפות אמש תחא תבב הליטנה תקספהמ ענמהל שי , תופורתה ראשב ומכ.Neurontin® מע Dilantin® וא

-נאהדא השמ -מייח ר"ד ומכ בחרנ וויסינ לעב באכב החמומ מע השיגפ מאתל קלמומ , רתויב רבצמל המיאתמה הפורתה תא רוחבל תנמ לע

md,cm , LMCC,CCFP, FRCPC,FABPM+R,

מיטרפ . אביש מייח מש לע יאופרה זכרמב באכ מוקישל זכרמה שאר , Dip Sports Med

רמושה לת , אביש מייח מש לע יאופרה זכרמה

מוי זופשא

'מייחל'יניב

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.מוקישא זכרמ

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530 5179 (03) 972 + :סקפ

3. חותינ

א. תיללכ הריקס

וכותב נמוט חותינ לש גוס לכ .TN לש באכה לע הטילשב ליעי אל אצמנ יאופרה לופיטה רשאכ קרפה לע הלוע תיגרוריוכוריונ תוברעתה רובעיש חותינה גוס תא הבר תוריהזב רוחבל הלוח לכ לע ,כל .רורא חווטל יאוול תועפותל וא מיכוביסל מינוכיס מגו מיילאיצנטופ תונורתו מייאתת הרודצורפ וזיא קידמ נפואב תוזחל ררד מוש ניא מירקמה לכב ליעי וניא מיחותינה יגוסמ דחא פא .תוכלשהה לכב תובשחתה רות .חתנמה יגרוריוכוריונה תווצה תא תודחיימה תויפיצפסה תוקינכטבו תיחמומב ,וויסנב תויולת הרודצורפ לכ לש תואצותה .הרקמ הזיאל

.ונבשחב ל"נה מירבדה לכ תא תחקל שי לופיט מירחוב רשאכ

:האבה הלבטב תורייאמו תומכוסמ תוילופיטה תוירשפאה נוגמ

ירלוקסו ורקים ץחל תתחפהל חותינ

ילנימגירטה בצעה שרוש ןיבל עגופה מדה ילכ יב Teflon® ארקנש ךותח דבל מיליתשמ חותינבירלוקסווריונה ץחלה לע לקמ חותינה

(רועה ךרד סרה) Percutaneous Rhizotomies

ילנימגירטה בצעל תרקובמ העיצפ תעצבתמ ש. (' foramen ovale ') תלוגוגה סיסב ךרדו יחלה ךרד טחמ מסיניכמ הז חותינב

:מיכרד שולשמ תחאב Gasserion ganglion לו

1) בצעה תמקרב ימיכ נפואב עגופו Gasserion ganglion ה ביבסש לחלל קרזומ לורצילג -רועה ךרד לורצילג תקירז

2) Percutaneous Balloon Compression Rhizotomy- גססנוכ ןולב תמקרב קיזמ, ינאכמ נפואב, ךכו ץחלולוגליוני Gasserion ganglion ה דיל סנכנו ןולב

בצעה.

3) Radiofrequency Rhizotomy- בצעה תמקרב קזנל תמרוג ימרת נפואבו Gasserion ganglion ל טסנכנו הדורטקלא

יפכ בצעה תמקרב לש קזנל תמרוגש ילנימגירטה בצעה שרוש לע תיטנגמ תכתמ לש תדקוממ הנירק- Gamma Knife Radiosurgery

תורחאה תוקינכט הרוקש

מיאצמנה ילנימגירטה בצעה לש מיקלחה לש העיצפ -ירפירפה ילנימגירטה בצעה לש (Nerve Blocks) בצע ימוח תמישו עוטיק, ךותיח

תלוגולוגל ץוחמ

חומה עזגל ותסינכל בורק ילנימגירטה בצעה שרושב העיגפו חותינב בצעה תפיפש Microsurgical Rhizotomy-

Microvascular Decompression Surgery-MVD -ירלוקסו ורקים ץחל תתחפהל חותינ. ב.

(' craniotomy ' ארקנ)ןזואה ירוחאמש רוזיאב מצעה לש נטק דואמ ךותיח לש הרודצורפ ללוכו תיללכ המדרה תחת עצובמ MVD חותינ

בצעה תא אצומו (חומה קלח) cerebellum ה רוזאב נובתמ, חותינ רדח לש פוקסורקים ךרד חתונמה רוזאה רחא בקוע חתנמה

(ילנימגירטה בצעה שרוש לש הסינכה רוזא)חומה עזגמ עיגמ אוהשכ ילנימגירטה

מילחלה ילנימגירטה בצעה ןיערגל רשפאמש רבד, ילנימגירטה בצעה שרוש לעמ ירלוקסווריונה ץחלה תא עיגרהל איה MVD חותינ תרטמ

קחרה עגופה מדה ילכ תא זיזהל תנמ לע מייפוקסורקים מילכב מישמתשמ .באכ לוטנ, ילאמרונו בצמל רוזחלו היה וב תוליעפה רתי בצממ

. בצעהו ץחולה מדה ילכ יב Teflon® רוזג דבלמ יושעה הז ומכ לתש טסנכה ידי לע תגשומ תותימצל ץחלה תתחפה .ילנימגירטה בצעה שרושמ

MVD חותינ ינפל

. בצעה שרוש לש הסינכה רוזיאמ קחרה זזומ מדה ילכ, MVD חותינ ךלהמב

Teflon® רוזג דבל לתשומ תותימצל היהת ץחלה תתחפהש תנמ לע

עובק נפואב ילנימגירטה

בצעה שרושמ ץחלה תדרוה ןה חותינה תואצות

חותינ רדח לש מייפוקסורקים Teflon® רוזגה דבלה לש לתשה טסנכה

מיטנייצפה בור .תוששואתה רדחל חקלנ אוהו המדרהמ טנייצפה תא מיריעמ .מירגסנ מצהו ךתחה, ירלוקסווריונה ץחלה תתחפה רחאל

נפואב ללכ ךרדב תגשומ TN לש באכב הלקה .תועובש המכ ךות האלמ תוליעפל מירזוח פוסבלו מימי רפסמל מילוחה תיבב מיראשנ

תופורת ידי לע לופיטל לק רתוי יהי אוהש נכתי, תינש רוזח באכה מא .חותינה רחאל מיעובש ךשמב הגרדה תוקספומ תופורתהו ידיימ

תויגרוריכוריונה תורודצורפהמ תחא תועצמאב בוש לפטל היהי ותינ .תמדוקה מעפב רשאמ

באכב חווט תכורא הלקהל רתויב הובגה לאיצנטופה תא הל שיו תינסרה אל הרודצורפ איה MVD ה חותינ

רפיש חותינה ידכ וות רותינ .מינפה לש השוחת רסוחו העימש דוביא ללוכה ילאינרקה בצעל קזנ לש רוביס לש וטק ווכיס שי ,נפוא לכב חותינה עוציבבש תוחיטבה תא

תויעב חתפל ווכיסה . CSF ה לש הפילדל מיליבומה יופירב ישוק וא תקלד ,חותינה רחאל מוהיז לש הרידנ תועראה מיללוק מירחא מינוכיס anesthesia dolorosa או (יבצע באכ) deafferentation גוסמ באכ לש תוחתפתה חותיפ לע עודי אלו טעמכו רומנ דואמ אוה מינפה לש השוחת (יחותינ וא יאופר יעצמא מוש י"ע הליעי הרוצב תולפוטמ תויהל תולוכי אלש תושוחת) MVD. חותינ עוציבל תדחוימ תויחמומ מע מיזכרמב ללכה נמ תאצוי הרוצב מירידנ מה תוחיפנ וא מומיד ,יחומ קבש נוגכ מירחא מייניצר מינוכיס

-מיאבה מידרשמה מע רשק רוצל קלמומ תיחותינ תוברעתה וזכל המיאתמ ת/דמעמו ה/תא מא קודבל תנמ לע

MD, Roberto Spiegelmann ומלגיפס וטרבור

Stereotactic Radiosurgery ל הדיחיה שאר

מילהנמה דעו רבח

(WSSFN) Stereotactic and Functional Neurosurgery ל תימלועה הרבחה

International Stereotactic Radiosurgery Society (www.isrsy.org) לש רבעשל אישנ

היגרוריכוריונל הקלחמה

רמושה לת ,אביש מייח מוש לע יאופרה זכרמה

52621 לארשי

0972 3 530 4420 :נופלט

0972 3 530 4420 :סקפ

תויורשפא לכ ואצומש אדוויל תנמ לע TNל רמסומ החמומ מע קעייתהל דואמ יאדכ , חותינ וורתפל מירבועש ינפל ,מירקמה בורב .ילאודידיניא הרקמ ותואל תומיאתמה תויביטברסנוקה לופיטה

md,cm , LMCC,CCFP, FRCPc,FABPM+R, -מייח ר"ד

. אביש מייח מוש לע יאופרה זכרמב באכ מוקישל זכרמה שאר , Dip Sports Med

מיטרפ:

רמושה לת ,אביש מייח מוש לע יאופרה זכרמה

מוי זופשא

'מייחל'יניב

19 רפסמ דרשמ

מוקישא זכרמ.

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0972 (03) 530 5179 :סקפ

ג. (Rhizotomies)בצעה לש סרה/העיצפ לש תורודצורפ

1. הגצה

חותינ תא רובעל מיצור וא מיבוט מידמעמו מה מילוחה לכ אל , TN לש באכה לע הטילשב לופיטב לשכנ תופורתב שומיש רשאכ

בצעל קיזהל איה נתרטמש בצעה לש סרה לש תורודצורפ ןה תוביטנרטלאה. MVD microvascular decompression surgery
באכב תינמז הלקהל ללכ ךרדב ליבומ בצעה דוקפתב יונישה .בצעה שרושב וא Gasserion ganglion ב ללכ ךרדב (rhizotomy) ילנימגירטה
םייק ןיידע TNל מרוגש ילנימגירטה בצעה לע ירלוקסווירונה ץחלה ,ןפוא לכב. TN לש

החמומ סע השיגפ מאתל ץלמומ ,ךלש יטרפה הרקמל רתויב המיאתמה Rhizotomy ה תרודצורפ תא רתויב הבוטה הרוצב רוחבל תנמ לע
-ומכ TNתב לופיטב בחרנ ןויסנ לעב באכב

md,cm , LMCC,CCFP, FRCPc,FABPM+R, -ןאהדאהשמ -מייח ר"ד
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rhizotomy רחאל rhizotomy לש הרודצורפ ינפל

והילע רזחל ןתינו MDS microvascular decompression surgery חותינ רשאמ עוציבל רתוי תוטושפ, תינכט, ןה rhizotomy לש תורודצורפ
רזוח TN לש באכה מא

(היזטסאראפ)הקיצמ השוחתב אטבתהל הלוכי השוחתה תייעב .מינפב השוחת תייעב איה וללה תורודצורפל הרושקש תיללכ יאוול תעפות
תושוחת-anesthesia dolorosa וא תרסיימו העובק באכ תשוחת מיחתפמ מיטנייצפ תורידנ מיתיעל .(היזטסאסיד)תבאוכ השוחתב וליפא וא
יחותינ וא יאופר יעצמא מוש י"ע הליעי הרוצב תולפוטמ תויהל תולוכי אלש

תורידנ הלוכי הסייעלה חוכ לש דרמא ירסייעל תיירקב תהלדל ליבירל ליכיש יערה תיירקב השוחת ןדבוא איה הרידנ תפסונ יאוול תעפות
balloon compression rhizotomies לש הרודצורפ רחאל דחוימב
הלוע ל"נה מיכויסה לש תוחיכשה ,תוינסרה תורודצורפ לע מירזוחש לככ .

2. Rhizotomies לש מיגוס

א. Percutaneous Glycerol Rhizotomy- רועה ךרד קרזומש לורצילג י"ע סרה

תיתרדש טחמ .תימוקמ המדרה תחת תעצובמ וז הרודצורפ

תנמ לע עבוצ רמוח מג קרזויו נכתי.(foramen ovale ה ךרד)תלוגלוגה סיסבב חתפה לא הפל ךומסש רועל תרדחומ (3.5" x 20 G)

ה תא ףיקמה ללחל קרזומ לורצילג ימיכה רמוחה , נכמ רחאל.X ינרקב השענש יפכ -קייודמב ןוכנה מוקמל תרדחומ טחמהש אדוויל

מיטנייצפה בורש ףא לע .מינפב העובק השוחת תייעבל ןוכיס מומינימ סע בצעל תיסחי ינוניב קזנל מרוג לורצילגה . Gasserion ganglion

תאז הרודצורפ לע רזחל ןתינ הז הרקמב .מינש המכ ךותב רזוח באכמ ולבסי סהמ יצח ,הרודצורפה תובקעב TN לש באכב הרימה הלקה מיווח
תורחא וא

.ילרסיגה ןוילגנגל טחמה תא ןווכל תנמ לע השענ X ינרק לש תומידב שומיש .ריהבו יגימצ ילקימיכ לזזו אוה לורצילג

ב. רועה ךרד ןולב לש ץחל ידי לע סרה-Percutaneous Balloon Compression Rhizotomy-

אצמנ לפוטמה רשאכ תעצבתמ וז הרודצורפ .ץחול ןולבב שומישב אוה רועה ךרד ילנימגירטה בצעה לש סרה עוציבל יביטנרטלא יעצמא

ץחומ אוהש דע חפונמ ןולבה .וחפנל ןתינש ןולב סע דחוימ רטטק לש רבעמ תרשפאמו רתוי הלודג תרדחומה טחמה .האלמ המדרה תחת

ןוילעה קלחב באכל דחוימב הליעי רועה ךרד סרהה לש וזה הרוצה .Gasserion ganglion בו ילנימגירטה בצעה שרושב ינאכמ ןפואב עגופו

השלוח תוחפל מיחתפמ מיטנייצפ הברה, נפוא לכב. ינעה תינרקב השוחת לש עובק נדבוא תמירגל רומנ יוכיס הל שיש ללגב (V1) מינפה לש לורצילג ידי לע סרהמה הרומח רתוי תובורק מיתיעל איה מינפה תשוחתב העיגפה תמרו וז הרודצורפ תובקעב הסיעלה ירירש לש תינמז

..

בצעה תא עצופו חפונמ וולבה נכמ רחאל. וולב מע רטטק מיסינכמ זאו תמקוממ נאכ תגצומה תירונצה.

ג. Radiofrequency Rhizotomy

לע, דירוה ררד רדחומה העגרה רמוח תחת תעצובמ תאז הרודצורפ. radiofrequency rhizotomy איה רועה ררד סרה עוציבל תרחא הדותמ ה ידי לע תמרגנה מינפב מהלש השוחתב הדיירה תמרו תדימ תא ראתל תנמ לע קיפסמ מירע תויהל מיבייח מיטנייצפהש פא יידע יוריג רישכמ ידי לע נחבנ הלש קיידמה מוקימהוGasserion ganglion ה ווויכל תנווכמ תדחוימה הדורטקלאה. radiofrequency הרוצל. בצעל ימרת קזנל תמרוגו תממחתמ הדורטקלאה, קזח העגרה רמוח לבקמ טנייצפהש נמזב, נכמ רחאל. מינפב טטר תשוחת רציימש שמח רחאל סג באכ אלל מיראשנ מילוחמה יעבר תשולשכ. באכה לע הטילשל רתויב רוראה חווטל העפשהה תא שי רועה ררד סרה לש תאז תייעב תמירגל נוכיס שיו מינפב השוחתל מרגנש קזנה תדימב היולת רורא חווטל החלצהה תדימ, נפוא לכב. הרודצורפה עוציבמ מינש . anesthesia dolorosa ל וא מינפב תבאוכ השוחת

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בצעל ימרת קזנ רצונ רכו Radiofrequency מרז ידי לע תממחתמ הדורטקלאה ילרסיגה נויילגנב תמקוממ תדחוימ הדורטקלא

ד. IN ORDER TO DETERMINE IF YOU ARE AN APPROPRIATE CANDIDATE FOR RADIOFREQUENCY LESIONING, YOU MAY WISH TO CONSULT WITH

ה. Stereotactic Radiosurgery (Gamma Knife)

המודה האצות-ותעיצפל תמרוגו ילנימגירטה בצעה שרושל תחלשנה תדקוממ הנרקה תרשפאמה השדח הקינכט החתופ, הנורחאל לפוטמה שאר לע (הדסק לש גוס) תרגסמ תמיש ידי לע תעצובמ Gamma Knife Radiosurgery. רועה ררד סרה לש תורודצורפה ראשל שרושל תונווכמש תיטנגמ הנירק לש תודקוממ מיינרק 201 לעמ שי משGamma Knife ב מקמתמ לפוטמה נכמ רחאל. MRI עוציב זאו מילפוטמה בור לצא תועובש המכ רותב TN לש באכה תא התיחפמו בצעה לש ותעיצפל נמז רובעכ תמרוג וז הרודצורפ. ילנימגירטה בצעה יאוול תועפותו מינפב השוחת נדבוא חותיפ לש מינוכיסב הילעל מורגל לולע קא רתוי תובוט תואצות גישהל לוכי הנירק לש רתוי הובג ונימ מידמלנ יידע וז הנירק לש מינוכיסהו רורא חווטל תלעותה לע מיטרפ. תורחא מייאבה מידרשמה מע רשק רוצל קלמז תיחותינ תוברעתה וזכל המיאתמ ת/דמעומ ה/תא מא קודבל תנמ לע

Roberto Spiegelmann, MD נמלגיפס וטרבור

Stereotactic Radiosurgery ל הדיחיה שאר

מילהנמה דעו רבח

Stereotactic and Functional Neurosurgery (WSSFN) ל תימלועה הרבחה

International Stereotactic Radiosurgery Society (www.isrsy.org) לש רבעשל אישנ

היגרוריוכוריונל הקלחמה

רמושה לת, אביש מייח שש לע יאופרה זכרמה

52621 לארשי

0972 3 530 4420 :נופלט

טקפ: +972 3 530 4420

1. Peripheral Trigeminal Nerve Blocks, ירפירפה ילנימגירטה בצעל (Nerve Blocks) בצע ימסוח תמישו עוטיק, ךותיח Sectioning and Avulsions

מישלח, דואמ מירגובמ מישנא תללוק ולא מישנא תצובק. ליעל ורכזוהש מיחותינה יכוביסל רתי תושיגר שי TN מ סילבוסהמ קלחל וקל וא רועל תחתמ שממ, תלוגלוגהמ מיאצויש בצעה יפנעל העיגפ אוה ילנימגירטה בצעב העיגפל תיסחי טושפ יעצמא. תיאופר מירערועמו תוליעי וללה תוקינכטהש תאז מע דחי. ולש עוטיקו ךותיח ידי לע וא לוהוכלא לש הקירז ידי לע בצעה לש וזה הדוקנה תא עוצפל ןתינ.הפה ןכלו רזוח TN לש באכה תובורק מיתיעל. עגפנה רזיאב השוחתה לש טלחומ וא רומח ןדבואל, ינמז ןפואב תוחפל, תומרוג ןה, ידימ ןפואב הלחמב טולשל ידכ תורחא תויחותינ תויוברעתה תועצבתמ

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1. Microsurgical Rhizotomy

דוע ליעי הז חותינ. מירושע ינפל גצוה אוהו TN לש באכב הטילשל ליעי יעצמא והז. חותינב ילנימגירטה בצעה שרוש לש סרהו הפישח microvascular decompression surgery מיחותינה מע בחרנ ןפואב ףלחוה הז חותינ, ןפוא לכב. ברועמ (V3) ןותחתה קלחהשכ רתוי קר מרוג הז חותינ. בצעה שרושל Microsurgical Rhizotomy ועצבי ןיידע מירידנ מירקמב. percutaneous rhizotomy techniques ן מיןפה לש ןותחתה קלחב יקלח השוחת ןדבואל

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Our practice specializes in treating a large variety of severe pain conditions relating to disease of the Joints, Tendons, Spine, and Nervous system as well as problematic Headaches and facial pains.

Our care is unique. We provide our patients with excellent medical care, such as the most appropriate medications and injections, as well as the latest cutting edge pain relieving Technologies that are integrated into a wholistic treatment approach.

Hebrew

Francais

ENGLISH

- With his love for Physical Medicine, Pain medicine, Sports Medicine, physics and technology, Dr. Adahan has distinguished himself as a reputable researcher, author, teacher, presenter, technician and skilled Medical and Rehabilitation Team Leader
- 18 Years experience and a talent for staying on the cutting edge of his area of expertise allow him to help many patients avoid the unpleasant prospect of surgery or injections by exploring new, effective, proven and original approaches to treatment based on the best possible scientific evidence.
- Broad expertise in Pain management that comes with being the Head of the Pain Rehabilitation Center in Israel's largest hospital
- American & Canadian Medical Specialist Credentials as well as Award winning research expertise in the field of Pain
- World Expert in the clinical use of Low Frequency ultrasound therapies with expertise

in laser therapies as well

- Also Certified by The Canadian Academy of Sports Medicine
- [Click here for more reasons to visit Dr Adahan](#)

The Pain Treatment Center

Dr. Haim Moshe Adahan, MD, LMCC



consultation by phone.

CONSULTATION PAR TELEPHONE

לחץ כאן כדי לקבל ייעוץ

You should consider a visit with Dr Adahan if you fall into one of the following 5 categories:

- 1-You have just been diagnosed with [trigeminal neuralgia](#) and you want to avoid taking potentially damaging medication over many years by using a therapeutic modality that ,via plausible scientific hypothesis, may in fact halt and/or reverse the usual progressive course of this illness that results in a need for an eventual neurosurgical intervention in about half of all cases over the long term.
- 2-You have had trigeminal neuralgia for some time and you are interested in trying to painlessly + gradually stop the medication you are taking either because of current problematic side effects or fear of futur side effects.
- 3-Your medication for trigeminal neuralgia has stopped working and you want to avoid entering a vicious cycle of ever ~~escalating medication dosages and do not want to take other and more medications~~ by using this new treatment as a complementary analgesic modality.

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4-You have been proposed Brain surgery and would like to try a less frightening and safer approach to treating your pain prior to accepting such a drastic intervention and its potential complications.

5-You have been proposed Radiofrequency lesioning , glycerol injection, or Gamma knife intervention of your nerve

~~The present field amongst doctors that goes like this, in the surgeon can not guarantee that he can cure you with no pain. but he can suggest it different! This is possible when it comes to trigeminal neuralgia.~~

Dr Adahan is the world expert on the use of Low Intensity Low Frequency Ultrasound Technology for the treatment of Trigeminal Neuralgia.

This technology, which is approved by the FDA , the EU, and the Israeli AMAR, is completely safe, has no known side effects or toxicity and is remarkably simple to use.

Dr Adahan offers a free 1 month trial of this technology to patients who consult him for their problematic trigeminal neuralgia.

When necessary, Dr Adahan may combine Painshield therapy with cutting edge Israeli Laser technologies and Unique Topical Ketamine preparations that he has brought from Canada to optimize results generally avoiding the problematic side effects and potential toxicities of Tegretol or other such Pain Drugs when they are taken as pills..

[Click here and go to the bottom of the page to see how others have succeeded in getting rid of their medication and avoid surgery with this new treatment.](#)

[CLICK HERE TO BENEFIT FROM MATERIAL THAT CAN HELP YOU TO GET THE MOST OF YOUR VISIT WITH DR ADAHAN FOR YOU TRIGEMINAL NEURALGIA PROBLEM](#)

Want to know more about Ultrasound and its role in treating Trigeminal Neuralgia and healing nerve injury? [Click here](#)

[Click here](#) to know more about Dr Adahan



Trigeminal Neuralgia_questionnaire.doc

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Le Centre de Gestion de la Douleur

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To see video testimonials of Patients who have been treated for their trigeminal neuralgia with the Painshield - [Click here -and go to the bottom of the page](#)

For your complete guide to Trigeminal Neuralgia - [Click here](#)

For animated guides towards Trigeminal Neuralgia and the minimally invasive and neurosurgical interventions available to treat it- [Click Here](#)

For more information about the progressive nature of the disease and the often escalating doses of medication needed to control the condition – [Click here](#)

For more information about the tiny nerve injury that is at the root of the problem - [Click here](#)

For more information on the Ultrasound effect on nerve healing - [Click here](#)

For more information on the low-energy ultrasound technology - [Click here](#)

For a list of common medications used to treat trigeminal neuralgia- [click here](#)

For more information on the PainShield device - [Click here](#)

For a video tutorial on how to use the Painshield to treat trigeminal neuralgia- [click here](#) (under construction)

For more information on compounding pharmacists and the helpful cremes than can make for you that , in combination with the painshield ,can give you significant relief of your pain- [click here](#)

For Trigeminal Neuralgia Support Groups and other resources:

The Facial Pain Association - [Click here](#)

Living with TN - [Click here](#)

Facial Neuralgia Resources - [Click here](#)



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Pain measurement tools

If your Mother Tongue is Hebrew--
Complete the 2 Hebrew
Questionnaires below before your
visit with Dr Adahan in order to get
the most out of your visit:



[BPI-Hebrew-
CURRENT 2 .
pdf](#)



[SF12 Hebrew.
pdf](#)



If you are ANGLOPHONE-
Complete the following forms
in English to make the most
of your visist with Dr Adahan



[BPI English Short form.
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דבאכב לופיטל עגונב אָהדא ר"ד מע פֿעייטהל דילע עודמ תוביסה

תיבה דומע

יטייעב באכב לופיטל תוקרזה 10.000 לעמ עציבו באכה מוחתב וויסינ תונש 18 לעב אָהדא ר"ד

זהו לפטמ אוה הב, לארשיב מילודגה מילוחה יתבמ דחאב באכ מוקישל הדיחיה להנמכ והכמ אָהדא ר"ד רתויב תושקה תוגרדהמ תויאבצו תויחרזא תועיצפב לופיטב סיפסונ סיאפור דירדמ

תימואל ייבה הריזב וגצוה מיינלקה וירקחמ. באכה תאופר מוחתל רושקה לכב תינחה דוחב אצמנ אָהדא ר"ד תיעוצקמה הימדקאה ברקב הדנקבו תירבה תוצראב מוסרפב ותוא וקיזו + laser - שומישבו באכב לופיטל דומנ רדתב דנואסרטלואה תויגולונכטב שומישב בר וויסינ אָהדא ר"ד ל (Shock Wave Therapy), מלה ילגב לופיטו

דותמ רתויב דל מיאתמה לופיטה תריחבב דתוא דירדהל אָהדא ר"ד לכוי ברה ונויסינו עדיה תועצמאב

תוינרמשהו תוילאנויצנונוקה תושישהמ לחה תומייקה תוירשפאה נוןגמ מימילשמ מילופיטב הלכו מייגרוריק מילופיט דרד תופסונ תוינרמש תושיש דינפב גיצי אָהדא ר"ד חותינל תנווכה וב הרקמב דבאכב לופיטל הביטנרטלאכ

לעב נכו טרופס תאופרל תידנקה הימדקאה מעטמ ראות לעב אָהדא ר"ד הצרא ותיילע מרט תירבה תוצראמו הדנקמ מוקיש תאופרב החמומ ראות 2005 תנשב

מילופיטל בויהב וביגה אל רשא מילוחב באכב לופיטב וויסינ אָהדא ר"ד ל מוחתב עוצקמ ישנא ברקב מילבוקמה באכב לופיטה לש יוקל לוהינו החנזה. העקשהל היואר דלש מייחה תוכיא תיזיפ הניחבמ זהו תיגולוכיספ הניחבמ זה דתואירב לע דוראה חווטל ועיפשי תידוקפתו

פאו יתועמשמ נפואב דבצמ תא מירפשם מניאש מילופיט קיספהל דילע דתואירבל קיזהל מיושע

יואר התא ול יעוצקמהו ישיאה לופיטה תא דל קינעי אָהדא ר"ד

באב לופיטל עגונב אהדא ר"ד ע מולשפלט תוצעיייתהקל ידכ אכ צחל



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10 Reasons to consult Dr Haim-Moshe Adahan for your problematic pain:

1- Dr Adahan has 18 years of experience and has performed over 10 000 injections to treat difficult pain problems

2-Dr Adahan is Head of the Pain Rehabilitation Center of Israel's largest hospital where he treats and teaches other Doctors to treat some of the most severe injuries in Military and Civilian Israelis

3-Dr Adahan is on the cutting edge of the field of Pain Medicine. His clinical research has been presented internationally and has awarded him prizes from several American + Canadian Professional Academies as well as the attention of the television and press internationally.

4- Dr Adahan is the world's foremost expert in the use of new Ultrasound technologies (Painshield) for the treatment of pain. He also is adept at using the newest Laser treatments and Shock wave therapy treatments .

5-Dr Adahan will, through his acquired experience and expertise, help guide you through the complex maze of possible conventional , conservative, surgical , and complementary therapies for your problematic pain. He can also help you decide as to whether you should consider more conservative treatment options if you have been suggested to have surgery for you problematic pain.

6-Dr Adahan is the leader of an interdisciplinary rehabilitation team of 12 professionals in Israel's largest rehabilitation campus and will be able to guide you towards the right rehabilitation resources for the management of the your problematic pain . Dr. Adahan is also certified by the Canadian Academy of Sports medicine as well as a recognized Specialist in Rehabilitation medicine in Canada and America prior to doing Alliyah in 2005.

7-Dr Adahan is used to seeing patients who have not responded to the treatments given by other Health Professionals, including that of other pain Specialists.

8- Your quality of life is worth investing in. Poorly managed Persistent Pain can and will adversely effect your long term psychological and physical health and will drain you of your strength to live your life to the fullest.

9- You should not continue treatments that do not help you substantially and/or that may be risky for your health

10-Dr Adahan will give you the kind of personal professional attention that you deserve



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[R.A., a 56 years old nurse and pianist, Petach-Tikva, ISRAEL](#)

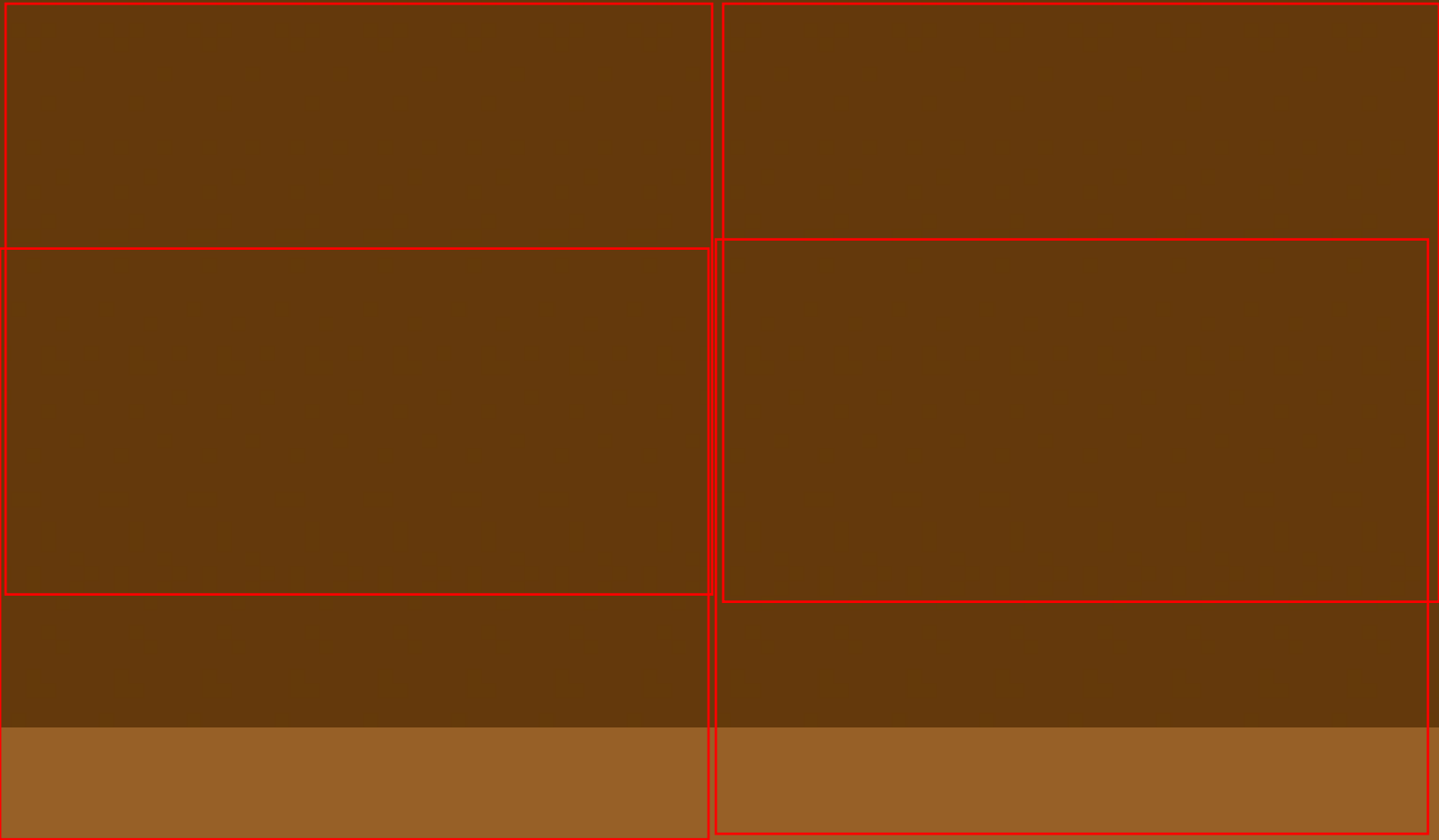
A year and a half ago I suffered from pain in the elbow area in both arms. I was diagnosed to have Tennis Elbow Tendonitis syndrome. With time the pain increased and become unbearable, it limited my daily activities and I wasn't able to drive, perform home tasks, carry a purse and even write. Of course I stopped playing the piano which was a major part of my life.

Conventional treatments such as medications and physiotherapy did not help and I refused getting steroid shots or consider surgery. My quality of life decrease significantly, I suffered at work and in the many other areas I was active at and become dependent on others.

Coincidentally, I approached Dr. Adahan who started that time evaluating the PainShield device. I started using this new portable ultrasound and after couple of weeks I started feeling some relief. Important to mention that I started with level 10 on the VAS pain scale and within a few months I reached level 0 in VAS scale which allowed me to return to full activity including playing the piano. I thank Dr Adahan and the Painshield for that.

Thank you,

R.A.



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Short Biography of Dr.

Adahan

- 1988: Graduated McGill University in Medicine
- 1994: Completed Residency in PM+R at the University of Ottawa.
- 1996-2000: Acting Assistant Professor, Department of Medicine – Division of PM+R at the University of Montreal.
- 1996: Winner of the AAPM+R « Young Investigator Award ».
- 1997: Diploma in Sports Medicine (Canadian Association of Sports Medicine).
- 1997: Winner of the P.A.S.S.O.R. research prize.
- 1998-99: Fellowship training in Interventional Pain Management, Université Catholique de Louvain, Brussels
- 1999: Winner of the Quebec Order of Radiologists Research Prize.
- 1999-2002: Acting Assistant Professor of the Department of Rheumatology at McGill University and staff at the prestigious Pain Clinic headed by Dr Ronald Melzack .
- 1999-2001: Managing Editor of the eMedicine Project – division of PM+R.
- 1995-2001: Principal investigator of three randomized controlled trials examining the efficacy of Supra-Scapular Nerve Blocks (VIA A NEW TECHNIQUE FOR THE BLOCK THAT I INVENTED)of which the largest is funded by the Arthritis Society of Canada.
- 1994: Principal investigator of a randomized controlled trial examining the relative efficiency of custom molded versus prefabricated foot orthoses in the treatment of patellofemoral pain in athletes.
- 2000-2002: Physiatrist in charge of Brain Injury and Trauma Rehabilitation Program – Jewish Rehabilitation Hospital, (McGill University affiliated).
- 2002-2008: Medical Director of the HTB Pain and Injury Rehabilitation Center. Quebec's largest free standing private Interdisciplinary Rehabilitation Center that employed 40 clinicians and received more than 1500 visits/week.
- 2005-Founder of the HTB-ED Industry sponsored Pain Clinical Research unit which is now ranked top Canadian recruiter field of Pain.
- 2008-Given the task of starting and directing Israel's first Fully Structured Interdisciplinary Interventional Pain Rehabilitation Unit at the Chaim Sheba Rehabilitation Campus

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Brief review of the currently available standard treatment for Trigeminal Neuralgia.

Medications are the first line of treatment for TN and include carbamazepine (Tegretol®), phenytoin (Dilantin®), gabapentin (Neurontin®) and baclophen (Lioresal®). As the disease progresses and pain becomes more frequent and severe, increased doses of medications are required which may lead to intolerable side effects and/or inadequate pain control. Each sufferer has differing tolerance to these medications and pain, but at least half will eventually find that medications do not adequately control their progressively worsening TN. The surgical procedures then considered are either microvascular decompression surgery or some form of nerve injury procedure (rhizotomies). Because ultrasound has the potential to heal injured nerve, we feel it is an intelligent choice for patients with Trigeminal neuralgia to attempt to reverse or at least slow the progress of there nerve injury.

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Crisci A.R., Ferreira A.L. Low-intensity pulsed ultrasound accelerates the regeneration of the sciatic nerve after neurotomy in rats. *Ultrasound in Med. & Biol.*, 2002; 28(10):1335–1341 [Full text](#)

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Effective Prevention of Microbial Biofilm Formation on Medical Devices by Low-Energy Surface Acoustic Waves[▽]

Zadik Hazan,¹ Jona Zumeris,¹ Harold Jacob,¹ Hanan Raskin,¹ Gera Kratysh,¹ Moshe Vishnia,¹ Naama Dror,^{1,2} Tilda Barliya,² Mathilda Mandel,² and Gad Lavie^{2*}

Nanovibronix Corporation, Nesher,¹ and Institute of Hematology and Blood Center, Sheba Medical Center, Tel-Hashomer,² Israel

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Low-energy surface acoustic waves generated from electrically activated piezo elements are shown to effectively prevent microbial biofilm formation on indwelling medical devices. The development of biofilms by four different bacteria and *Candida* species is prevented when such elastic waves with amplitudes in the nanometer range are applied. Acoustic-wave-activated Foley catheters have all their surfaces vibrating with longitudinal and transversal dispersion vectors homogeneously surrounding the catheter surfaces. The acoustic waves at the surface are repulsive to bacteria and interfere with the docking and attachment of planktonic microorganisms to solid surfaces that constitute the initial phases of microbial biofilm development. FimH-mediated adhesion of uropathogenic *Escherichia coli* to guinea pig erythrocytes was prevented at power densities below thresholds that activate bacterial force sensor mechanisms. Elevated power densities dramatically enhanced red blood cell aggregation. We inserted Foley urinary catheters attached with elastic-wave-generating actuators into the urinary tracts of male rabbits. The treatment with the elastic acoustic waves maintained urine sterility for up to 9 days compared to 2 days in control catheterized animals. Scanning electron microscopy and bioburden analyses revealed diminished biofilm development on these catheters. The ability to prevent biofilm formation on indwelling devices and catheters can benefit the implanted medical device industry.

Indwelling device-related infections constitute a major cause of morbidity and mortality in hospitalized patients, adding considerably to medical costs. Microbial biofilms readily develop on all types of devices, urinary, endotracheal, intravenous, and other types of catheters and implants inserted into more than 25% of patients during hospitalization. The incidence of bacterial infections in patients with urinary catheters is approximately 5 to 10% per day, with virtually all patients who undergo long-term catheterization (≥ 28 days) becoming infected (13, 14, 17).

The first stage in biofilm formation from planktonic microorganisms is attachment to solid surfaces (6). Attachment stimulates microbial aggregation and proliferation to form microcolonies. The colonies excrete an encasing exopolysaccharide “slime,” which consolidates the attachment to surfaces, and the microaggregates differentiate into characteristic biofilms (20). Quorum-sensing molecules that generate concentration gradient-dependent signals that control and alter expression of a large number of genes also aid biofilm differentiation (15, 25). Encasing the extracellular polysaccharide matrix of biofilms regulates exchange of ions and nutrients with the surrounding environment. This regulation contributes to increases of up to 1,000-fold in biofilm resistance to antibiotics compared to planktonic bacteria (9, 11) and protects the biofilms from biocides, surfactants, and predators. Microbial biofilms also present serious challenges to the immune system because expression of bacterial antigens within the encasing polysaccha-

ride matrix is suppressed and the colonies are highly resistant to phagocytosis by polymorphonuclear cells (12). Altogether these properties render biofilms exceedingly difficult to eradicate and explain the severity, persistence, and high levels of morbidity associated with the infections that they produce.

The harsh and potentially fatal consequences of microbial biofilm infections generated efforts to prevent their formation, particularly on indwelling medical devices using chemical and mechanical approaches. Catheters coated with hydrogel, silver salts, and antimicrobials have been evaluated; however, they provide minimal reduction in infection incidence (21). Mechanical approaches to preventing biofilm formation have utilized ultrasonic energy, yet the focus has thus far been on increasing biofilm sensitivity to antibiotics (18). The combination of ultrasound with antibiotics was found effective only in reducing the burden of *Escherichia coli* biofilms in animal models, falling short of providing a comprehensive solution to the biofilm problem (3).

We devised an innovative approach in which we generate low-energy elastic acoustic waves of practically nonthermal range from electrically activated piezo ceramic elements. The vibration energy is transmitted directly to indwelling medical devices in an integrated unit. Our aim was to achieve dispersion of the acoustic energy on entire surfaces of indwelling medical devices with different consistencies and structures. We analyzed the physical and power requirements for harnessing these waves to prevent microbial attachment and biofilm formation. The findings were consolidated into piezo actuators generating low-power acoustic waves at frequencies ranging from 100 to 300 kHz. The results of studies evaluating the efficacy of these actuators in preventing biofilm formation on indwelling medical devices from several microorganisms, in vitro and in animal models, are presented.

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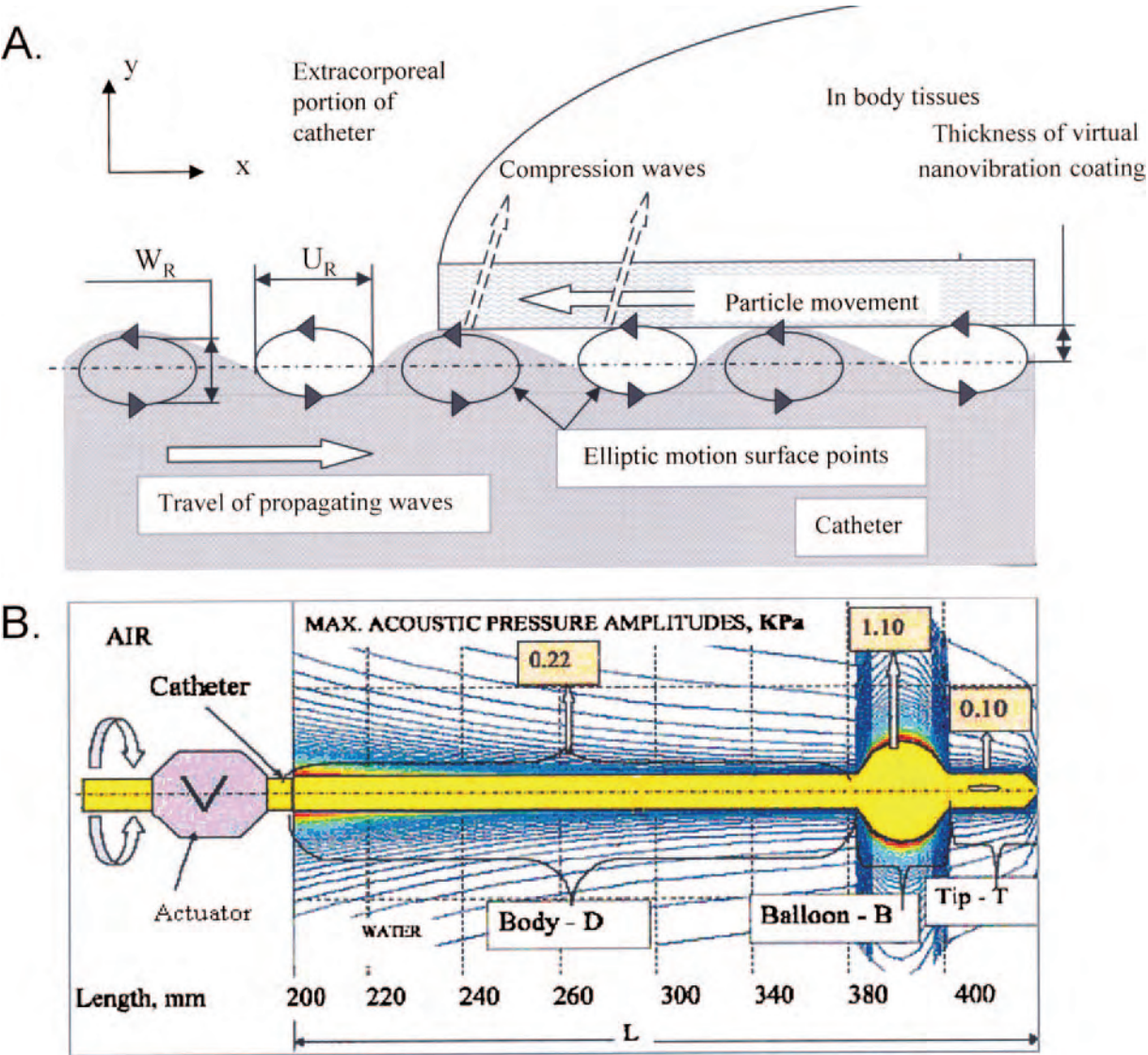


FIG. 1. (A) Schematic illustration of the modes of dispersion of surface acoustic waves on solid surfaces. Horizontal particle displacement (U_R) and another transversal compression wave component (W_R) are indicated. (B) Schematic illustration of acoustic pressure amplitude distribution of the coating nanowaves among the different parts of a urinary catheter (body, balloon, and tip). Max., maximum; L, length.

MATERIALS AND METHODS

Generation and dispersion of acoustic vibration energy on the surfaces of catheters. A device generating surface acoustic waves (SAW) and capable of transmitting the vibration energy directly onto indwelling catheters has been constructed. A battery-powered electronic driver delivers periodical rectangular electrical pulses to an actuator harboring a thin piezo ceramic plate. Piezoelectric vibrations are generated in the actuator at frequencies of 100 to 300 kHz with an acoustic intensity of 200 mW/cm² and amplitudes of 300 to 800 nm.

Low-energy SAW spread from an actuator to catheters, covering all surfaces with waves at amplitudes between 0.2 and 2 nm. These waves acquire two vectors as shown in Fig. 1A. A longitudinal vector spreads parallel to the wave propagation x axis along the catheter surface, triggering horizontal particle displacement. Another transversal compression wave component develops on the y axis in the direction of surrounding tissues or fluid. Consequently, all catheters are covered with a virtual vibrating coat (24).

The acoustic pressure amplitudes of the waves vary on different parts of urinary catheters (body, balloon, and tip) as shown in a simulation of their measurements (Fig. 1B). The largest transversal vector directed perpendicular to the catheter surface is detected around the balloon with maximal power intensities of ≤ 1.1 mW/cm². These noncavitational power intensities

TABLE 1. Bioburden analyses (CFU/cm²) of microbial biofilms developing on 16Fr Foley catheters treated with SAW^a

Microbial species	Bioburden (CFU/cm ²) of microbial biofilm developing on 16Fr Foley catheter		SD ^b	Log reduction ^c	P value ^c
	Control	SAW-treated			
<i>Escherichia coli</i>	4.07E+04	6.55E+03	1.84E+05	−0.79	0.009
<i>Candida albicans</i>	1.52E+04	9.02E+02	1.13E+04	−1.22	0.050
<i>Proteus mirabilis</i>	6.90E+04	4.87E+03	1.20E+05	−1.15	0.001
<i>Enterococcus faecalis</i>	4.42E+04	7.78E+03	2.26E+05	−0.75	0.015

^a Three-centimeter sections were prepared from each catheter, sonicated at 20 KHz and 3 to 4 W in two 30-second pulses to shed the catheter-associated biofilms and disperse them in solution for titration. Microbial counts correspond to overall load on 3-cm-long catheter sections.

^b Standard deviations refer to differences in bacterial loads between the control and the SAW-treated in the three repetitions of each analysis.

^c Log reduction values and P values compare the bioburdens for control and SAW-treated catheters.

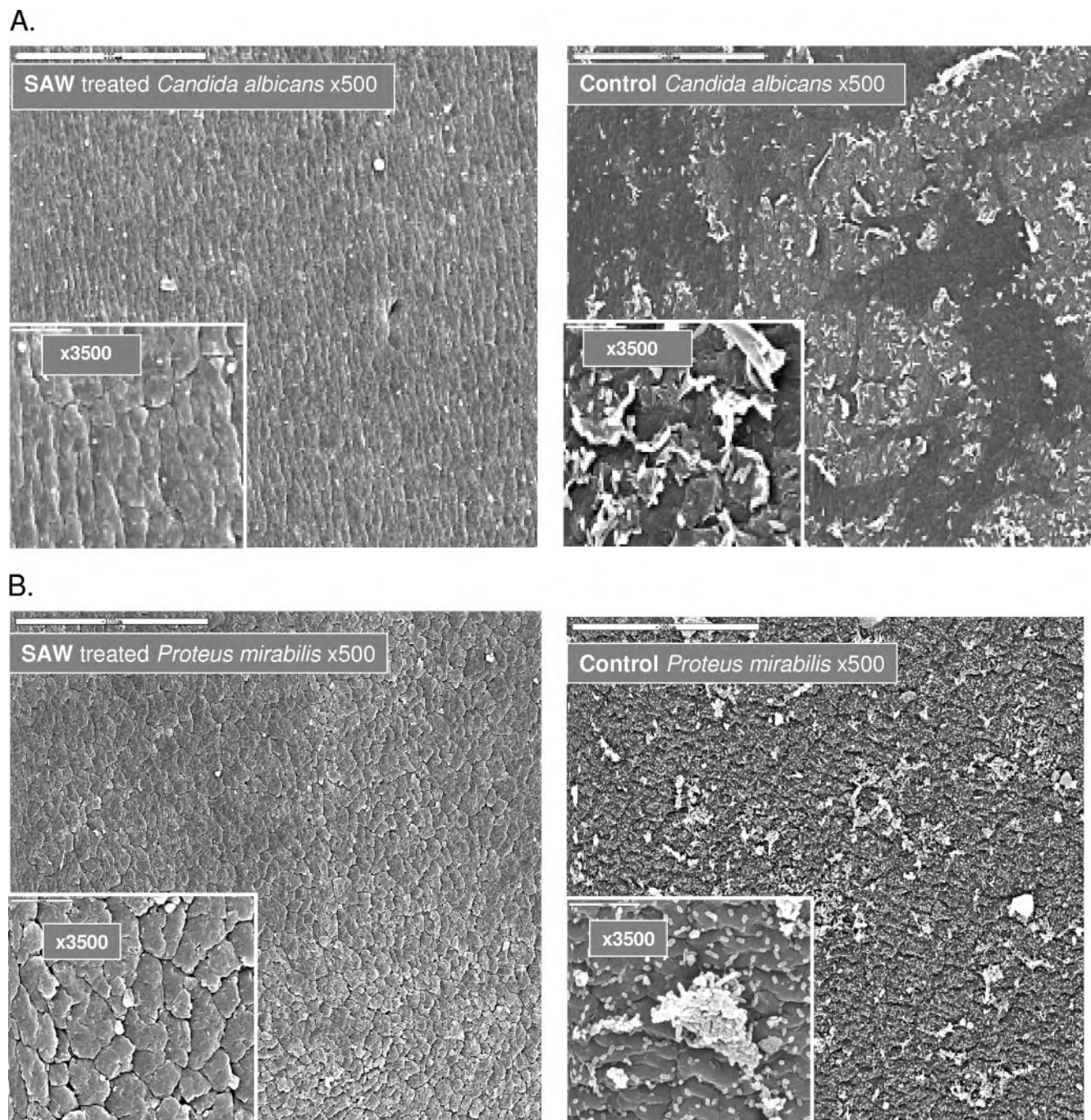


FIG. 2. Scanning electron microscopic analyses of external surfaces of SAW-vibrated 16Fr urinary catheter segments, on which several types of bacteria were passed in culture. Catheter segments, 6 cm long in 25-ml tissue culture flasks (Corning, N.Y.), were attached to a piezo resonator that generated acoustic pressure amplitudes ranging from 0.16 kPa at the edge of the catheter to 0.21 kPa at the center. Fresh media containing 10^3 CFU/ml of several types of bacteria (from ATCC) were pumped continuously from chemostats at 0.5 ml/min and a temperature of $\sim 30^\circ\text{C}$ for 3 days. The segments were fixed in 4% buffered formaldehyde, rinsed four times with PBS, and dehydrated incrementally with 25% to 100% aqueous ethanol gradients. Following drying in a Bio-Rad C.P.D 750 critical point dryer, the samples were mounted on metal stubs and coated with a gold layer, and three different areas on each catheter were examined by SEM. Surfaces of SAW-treated catheters (left panels) are compared to nontreated controls (right panels).

are 3 orders of magnitude lower than the thresholds beyond which cavitation is produced (frequency $f = 100$ kHz at acoustic intensities of 0.5×10^3 to 2×10^3 mW/cm 2) (5, 8).

Evaluation of biofilm prevention on urinary catheters by SAW in vitro. Sections of 16Fr Foley catheters 6 cm long (siliconized latex; Unomedical, Den-

mark) were attached to piezo actuators, sterilized with isopropyl alcohol, and placed in 25-ml tissue culture flasks (Corning) through an opening created at the top of the flask. Several commercial microbial strains (*E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 19433, *Candida albicans* ATCC 10231, and *Proteus mirabilis* ATCC 4630 supplied by Hylabs, Rehovot, Israel) were cultured over-

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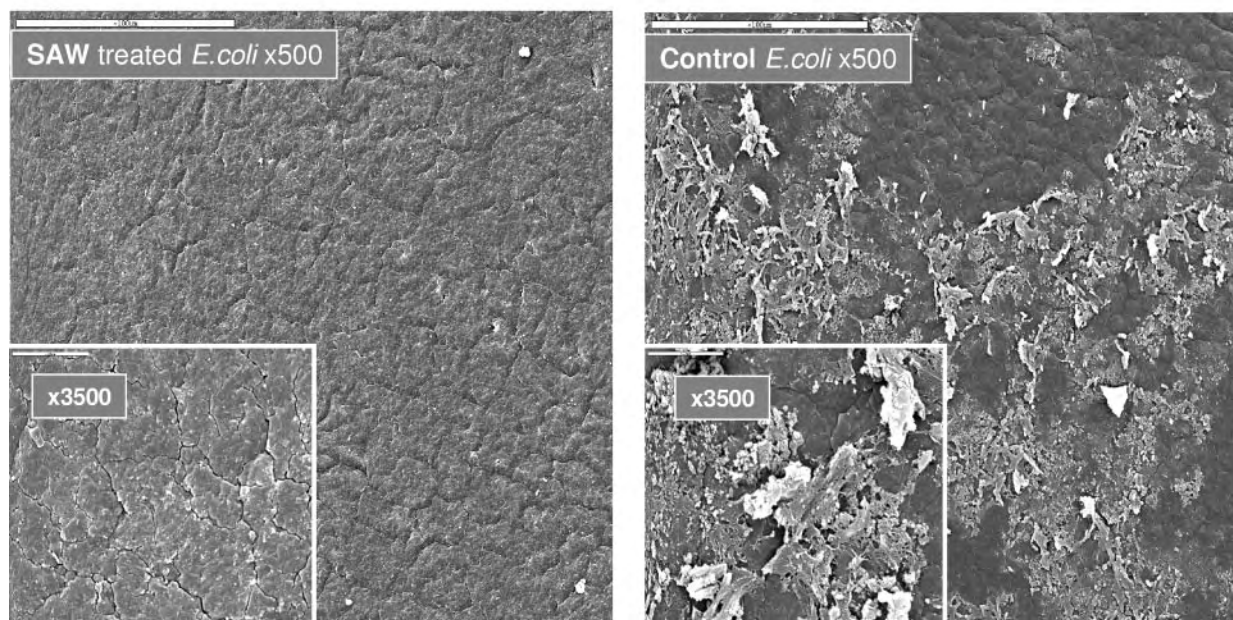


FIG. 2—Continued.

night in Bacto tryptic soy broth (TSB) (Difco). The log-phase cultures were brought to a concentration of 10^9 CFU/ml determined by optical density at 640 nm and confirmed by plate counts. The selected bacteria were brought to a concentration of 10^3 CFU/ml in a mixture of (i) 50% of a solution containing 8 g of TSB and 8 ml fetal calf serum (Gibco) in 1 liter of phosphate-buffered saline (PBS) (Gibco) and (ii) 50% heat-sterilized human urine from a healthy donor and placed in a chemostat to which the flasks were connected and sealed with plastic covers. The media were passed over the catheters in the flasks continuously for the 3-day duration of each experiment. Flow was achieved via a peristaltic pump at a rate of 0.5 ml/min under a temperature of $\sim 30^\circ\text{C}$ with the input medium replaced daily (batch system). Signals for surface acoustic nanowaves were monitored twice daily in the active chambers using a highly sensitive hydrophone. After 3 days, the catheter segments were rinsed and cut into two halves. One half was subjected to sonication at 20 kHz and 3 to 4 W output (model 550 sonicator; Fisher Scientific) to shed the biofilm off the catheter. The overall bioburden on catheter surfaces was assayed by plate counts on blood agar of removed biofilm mass from 3-cm sections of the catheters. Other sections were left intact for biofilm assessment by scanning electron microscopy (SEM).

Preparing catheter samples for SEM. Catheter samples were fixed in 4% buffered formaldehyde (Frutarom, Israel) and rinsed four times with phosphate-buffered saline (GIBCO). Critical drying was performed with ethanol at concentrations increasing from 25% to 100% in double distilled water. The samples were dried in a critical point dryer (Bio-Rad C.P.D 750), mounted on metal stubs, and coated with a gold layer. Three different points were examined in each catheter by SEM at three magnifications: $\times 500$, $\times 1,000$, and $\times 3,500$.

Catheters removed from rabbit urinary bladders were sectioned into 1-cm-long fragments of the body, balloon, and tip of each catheter and processed for SEM as indicated above. The outer and inner surfaces were evaluated separately at three different magnifications, $\times 500$, $\times 1,000$ and $\times 3,500$, from four different animals in each experimental group.

Evaluation of SAW effects on microbial biofilm formation on urinary catheters in rabbits. The animal studies were approved by the Animal Care and Welfare Committee of the Israel Ministry of Health. A single piezo actuator was attached to the extracorporeal portion of 10Fr siliconized latex Foley urethral catheter bodies (Unoplast), sterilized with 70% ethanol, and dried. New Zealand White rabbits, 3 to 4 months old and weighing 3.5 to 5.5 kg, were anesthetized with a mixture of 1:1 ketamine (25 mg/ml) and xylazine (20 mg/ml) (0.7 ml/kg of body weight). The perineal region was disinfected with 70% ethanol and antiseptic povidone iodine, the catheters were inserted through the meatus, and the internal balloon was inflated with 3 to 4 ml sterile saline. The rabbits were dressed with a coat-like harness attached to an overhead wire which ran across the top of

the cage, enabling limited forward backward movements while preventing the rabbits from pulling out the catheters. A sterile collecting bag was connected to the catheter and replaced daily when urine samples were collected. The extracorporeal portion of the catheter was attached to swing-like devices hanging from the ceiling. These devices allowed free mobility of the catheter with movements of the rabbit and prevented friction with the cage floor, premature catheter detachment, and excessive contamination with feces.

Following catheterization, the piezo elements were activated with power from an alternating current source and remained active throughout the full duration of the experiments (7 days in one experiment, up to 8 days in a second experiment, and 9 days in a third experiment). Catheters showing markedly decreased or no urine output for 12 h were unblocked using sterile flexible wires. Urine was collected once daily in a sterile manner from the bag throughout the experiment, serial dilutions were performed in PBS, 100 μl was dispersed evenly on blood agar plates (Hylabs, Rehovot, Israel), and bacterial counts were performed after 24 h. Animals that developed bacteriuria of $>10^5$ CFU/ml were excluded in accord with Animal Care Committee requirements.

Induction of guinea pig erythrocyte aggregation by mannose receptor-specific adhesion of uropathogenic *E. coli* bacteria bearing type 1 pili. A strain of uropathogenic *E. coli* bacteria bearing type 1 pili and displaying the FimH lectin was selected from clinical isolates at the microbiology laboratory of the Sheba Medical Center. The bacteria were analyzed for the ability to form biofilms and the ability to induce guinea pig red blood cell (RBC) aggregation. Bacteria (10^9 /ml) were applied to a 4% guinea pig erythrocyte suspension in saline (0.9% NaCl) in 50-mm Miniplast petri dishes to which a single SAW actuator has been attached at the external bottom surface of the plates. D-Mannose at a final concentration of 50 mM was used to confirm mannose receptor specificity of the interaction with FimH. The plates were monitored microscopically at room temperature after 15 min, 1 h, and 3 hours for the effects of SAW on bacterial adhesion-mediated aggregation and photographed with a Nikon digital camera.

Statistical analyses. The two-tailed Student *t* test was used for determination of statistical significance with a *P* of <0.05 as a cutoff.

RESULTS

Prevention of microbial biofilm formation by surface acoustic waves. We examined the effects of low-energy SAW on biofilm formation by four common clinically relevant types of microorganisms on several types of surfaces, including 16Fr

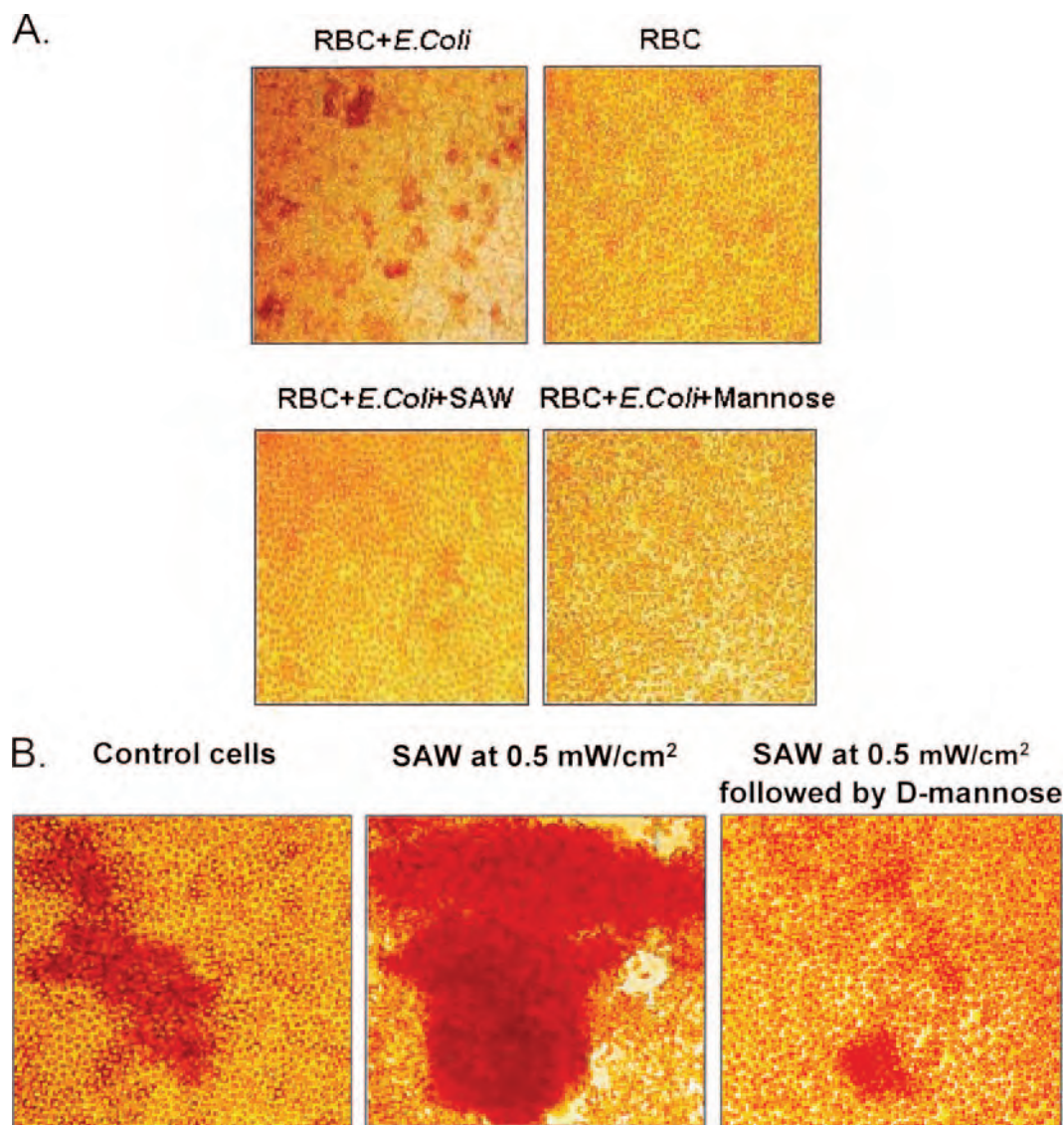


FIG. 3. (A) Prevention of guinea pig RBC aggregation induced by adhesion of type 1 pilus-positive *E. coli* bacteria. Surface acoustic waves at a power intensity of 0.2 mW/cm² are shown to effectively prevent mannose receptor-specific adhesion of bacteria to RBC and their subsequent aggregation. Specificity was confirmed with 50 mM D-mannose. (B) Enhancement of *E. coli*-induced guinea pig RBC aggregation by high-energy SAW. Surface acoustic waves applied at a power intensity of 0.5 mW/cm² are shown to enhance mannose receptor-specific bacterial adhesion to RBC. The samples in panels A and B were photographed 3 h after administration of bacteria and initiation of treatment with SAW. Exceedingly large RBC aggregates formed, as shown in Fig. 3B (middle panel), which were susceptible to dissociation with D-mannose (Fig. 3B, right panel).

urinary catheters to which actuators were attached. Bacterial bioburden on catheter surfaces, measured by plate counts, revealed marked reductions in the biofilm loads formed on surfaces of SAW-treated catheters ranging from -0.75 to $-1.22 \log_{10}$ ($P \leq 0.05$, $n = 3$) relative to controls (Table 1).

Other segments of these catheters were examined by scanning electron microscopy, and results obtained with *Candida albicans*, *Proteus mirabilis*, and *E. coli* are presented in Fig. 2. The SAW treatment effectively reduced biofilm formation, leaving catheters virtually clean of adherent microorganisms, irrespective of the types of bacteria that were examined. Similar prevention of microbial cell adhesion and biofilm formation was also noted on glass rod surfaces attached with piezo actuators (data not shown), indicating that these ele-

ment-generated elastic waves can be adjusted to prevent microbial adhesion and biofilm formation on surfaces with different consistencies and shapes.

Surface acoustic waves interfere with adhesion of planktonic microorganisms to cellular surfaces. Our analyses of mechanisms by which SAW interfere with bacterial biofilm formation focused on the hypothesis that SAW target the adhesion of planktonic bacteria to surfaces, the first step in the biofilm formation process. To evaluate the effects of SAW on bacterial adhesion, we used the mannose receptor-specific adhesion of uropathogenic *E. coli* bacteria to guinea pig erythrocytes as a model; the adhesion occurs via type 1 pili, FimH lectin and culminates in RBC aggregation (22). In this system, bacterial adhesion occurs rapidly, can be easily monitored mi-

TABLE 2. Time to bacteriuria in rabbits with 10Fr Foley catheters and SAW-generating piezo actuators^a

Rabbit	Bacterial titer (CFU/ml) on:								
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
SAW-treated rabbits									
163	0	0	0	0	0	0	0		
229	0	0	0	0	0	0	0	0	0
265	0	0	0	0	0	10 ⁴	10 ⁶		
143	0	0	0	0	0	3 × 10 ³	2 × 10 ⁴		
Control rabbits									
28	0	1.4 × 10 ⁷	5 × 10 ⁷						
31	4	10 ⁴	5 × 10 ³	10 ⁴	0	0	8 × 10 ⁸	2.5 × 10 ⁸	
150	0	6	4 × 10 ⁶	10 ⁸					
144	70	10 ⁶	5 × 10 ⁶						

^a Rabbits had 10Fr Foley catheters inserted. The catheters were attached to SAW-generating piezo actuators at the extracorporeal body of the catheters. Animals that developed bacteriuria were removed and their participation in the experiments was terminated due to limitations imposed by the Animal Welfare and Care Committee.

croscopically in real time, and enables an easy and accurate monitoring of the reversibility of the acoustic wave effect upon cessation of the treatment.

Vibration energy-generating actuators were attached to the external bottom surfaces of 50-mm Miniplast petri dishes in which uropathogenic *E. coli* bacteria were cocultured with guinea pig RBC. Power intensities of 0.1 and 0.2 mW/cm², generating vibration frequencies of 95 kHz and 220 kHz with acoustic pressure amplitudes of 0.1 and 0.22 kPa, respectively (equivalent to those measured on the tip and body of the urinary catheter), were applied. RBC aggregation mediated by bacterial adhesion was monitored; it became detectable in control dishes 12 min ± 3 min after administration of the bacteria and was monitored for hours. Figure 3A shows that SAW effectively prevented RBC aggregation at these two power intensity outputs throughout the follow-up time. The findings support our hypothesis that SAW interfere with lectin-mediated adhesion of planktonic bacteria to substrates.

We deactivated the SAW treatment and continued to monitor the plates with time-lapse photography. Guinea pig erythrocyte aggregation resumed 10 min ± 4 min after SAW termination, a rate similar to RBC aggregation in control plates (12 min ± 3 min; difference not significant). These findings indicate that inhibition of RBC aggregation by SAW is mechanical, readily reversible following SAW deactivation, and does not diminish the functionality of the FimH lectin on fimbriae. The bacterial mechanism for adhesion to RBC and other cells is thus not damaged by SAW. Once aggregation has taken place, RBC aggregates could no longer be dissociated by resumption of the SAW treatment (not shown), although it was reversed by D-mannose.

We next examined the correlation between levels of SAW energy that were applied and *E. coli*-induced RBC aggregation. SAW activated with 0.05 to 0.20 mW/cm² effectively prevented RBC aggregation (Fig. 3A); however, increasing the output to beyond a 0.35-mW/cm² threshold converted the inhibition into a significant enhancement of bacterial attachment. Exceedingly large RBC aggregates formed as shown in Fig. 3B, which were susceptible to dissociation with D-mannose (Fig. 3B) and gradually dissolved upon cessation of the SAW treatment (not shown). Hence, SAW applied at power intensities beyond approximately 0.35 mW/cm² can activate FimH force sensor activity in a manner

similar to force sensor activation seen when shear force is applied to uropathogenic *E. coli* bacteria (22).

Prevention of microbial biofilm formation on urinary catheters with acoustic nanowave actuators in an animal model in vivo. The ultimate preclinical determination of whether SAW-generating piezo actuators can interfere with microbial biofilm formation on urinary catheters in clinical settings is in animal studies. We inserted 10Fr Foley catheters attached with a piezo actuator at the extracorporeal portion of the catheter into the urinary bladders of male rabbits in a sterile manner. The devices were activated for up to 9 days in four of eight tested rabbits (in three separate experiments). Urine samples were collected daily, the bacterial load was titrated, and time to bacteriuria was determined. Urine samples from rabbits with SAW-treated catheters remained sterile for 5, 7, and 9 days (26 cumulative days of sterile urine) despite the extensive contamination of the perineal area with feces. Furthermore, the bacteriuria that did develop in some rabbits was mostly of low titers, whereas three of four control rabbits developed bacteriuria of >10⁶ CFU/ml within 2 or 3 days and the fourth had a titer of >10⁸ CFU/ml on day 7. The average number of days to development of urinary tract infection, defined as bacteriuria of >10⁵ CFU/ml, was 7.3 ± 1.3 days for the SAW-treated animals versus 1.5 ± 0.6 days in the nontreated controls (*P* < 0.0009 by two-tailed Student's *t* test; *n* = 4) (Table 2).

At the end of the experiments, the animals were sacrificed, the bladder and urethra were cut open, and the catheters were removed carefully, avoiding disruption of the biofilms. Biofilm content was examined by SEM. Analyses of the internal surfaces of recovered catheters revealed strong inhibition of bacterial biofilm formation on the surfaces of catheters treated with SAW (Fig. 4A). In contrast, control group catheters were covered with various densities of microbial biofilms despite the shorter durations of catheterization (in two of the animals, the catheters were in place for only 3 or 4 days) (Fig. 4B).

Evaluation of the integrity of mucous membranes by histological and ultrastructural analyses in all control and SAW-treated animals revealed that the treatment with SAW did not produce any histopathological changes. Furthermore, uroepithelial integrity was found to be less affected by trauma and

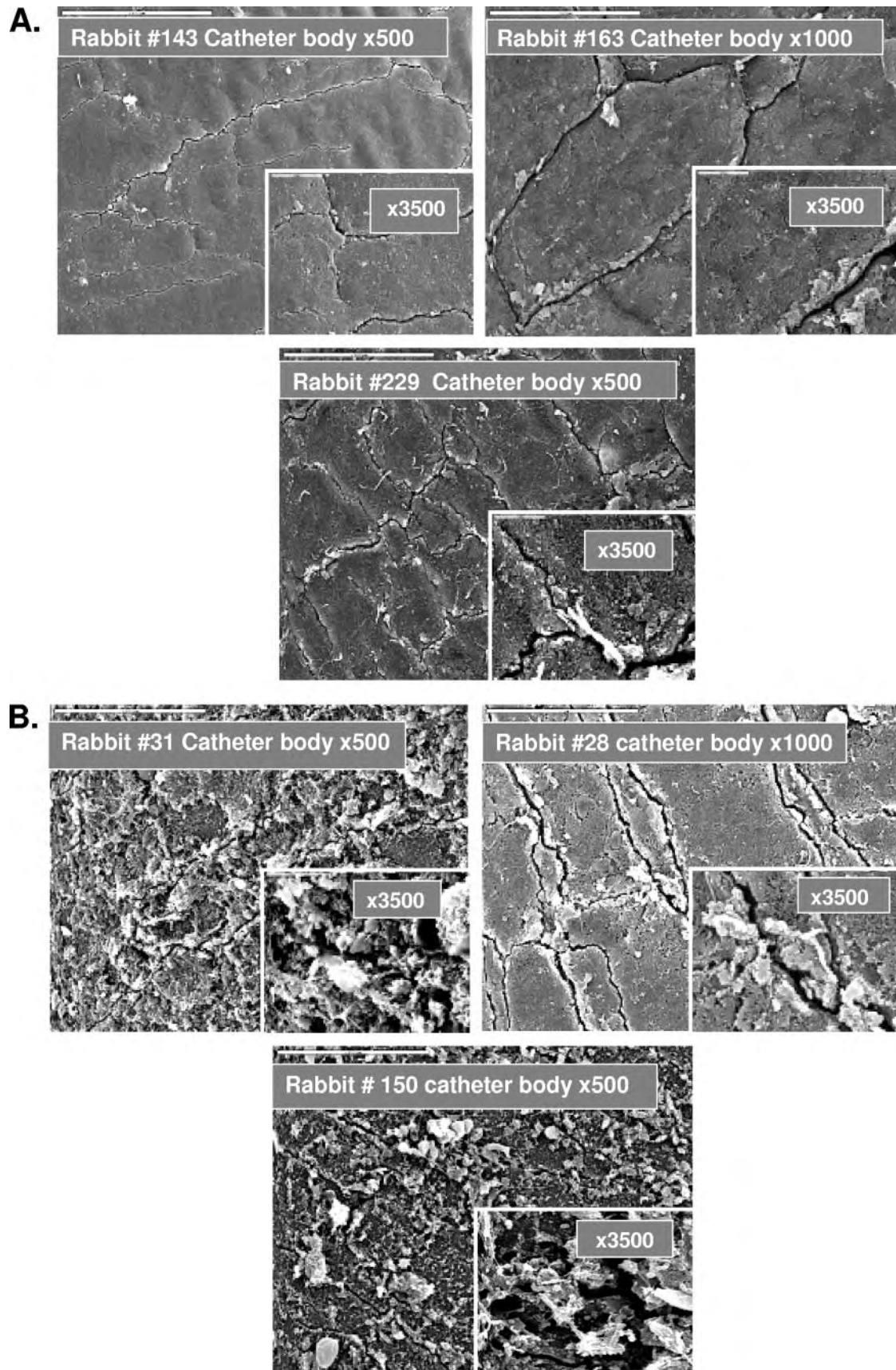


FIG. 4. SEM analyses of the inner surfaces of catheters recovered from rabbit bladders following treatment with SAW in vivo. Catheters were removed from rabbit urinary bladders, sectioned (into body, balloon, and tip), and processed for SEM as described in the legend to Fig. 2. (A) SAW-treated animals and (B) control animals.

better conserved in the SAW-treated animals than in the controls (data not shown).

DISCUSSION

The remarkable flexibility by which microorganisms adapt to changing environments or become insulated from environmental hazards has been the core of shortcomings in the ability of chemical approaches to prevent microbial biofilm formation on implanted medical devices. Efforts to eradicate biofilms therefore include mechanical approaches, which thus far have mainly been aimed at increasing the penetration of antibiotics into microbial colonies (3, 18).

We have contemplated utilization of mechanical vibration energy to interfere with early events in the biofilm development process—the adhesion of planktonic microorganisms to surfaces. By preventing adhesion, we sought to abort their subsequent firm attachment to substrates (1), gene expression reprogramming, and synthesis of the corresponding protein products that transform the lifestyle of microorganisms from the planktonic to sessile form (2, 4, 19). We also speculate that chaotic microstreaming produced in fluids by the ongoing vibrations hampers the development of coherent concentration-dependent gradients of quorum-sensing molecules. Disruption of such gradients is likely to interfere with cell-cell communications between microorganisms, virulence factor production, and other postattachment biofilm developmental processes. The outcome is prevention of colony differentiation and biofilm formation (7, 10, 16).

We show that low-energy elastic acoustic waves transmitted directly to extracorporeal portions of implanted medical devices can interfere effectively with attachment of planktonic microorganism to surfaces and prevent biofilm formation for extended time intervals. The mechanical nature of this treatment implies that the elastic waves must be powered continuously throughout the duration of device implantation to prevent attachment of planktonic bacteria. Disruption of the vibration energy is found to promote renewed adhesion of bacteria to these surfaces, indicating that the effects of SAW are readily reversible and do not diminish the functionality of bacterial adhesion mechanisms. For example, the fimbrial FimH lectin of uropathogenic *E. coli* allowed attachment of *E. coli* to guinea pig RBC following disruption of SAW.

A unique feature of this approach is the effectiveness of minute power intensities in preventing bacterial attachment to substrates. Analyses of mannose receptor-mediated adhesion of *E. coli* to guinea pig erythrocytes reveal that power densities ranging from 0.05 to 0.20 mW/cm² with amplitudes of ≤ 3 nm completely prevent erythrocyte aggregation. In contrast, SAW intensities of >0.35 mW/cm² generate opposite effects, inducing strong FimH-mediated adhesion of the bacteria and enhanced RBC aggregation (Fig. 3B). This response to high SAW intensities bears similarities to the response of these bacteria to shear stress. Under stress, the FimH lectin has been reported to act as a force sensor switching bacterial loose adhesion into a firm attachment (22). Application of high-SAW power intensities to *E. coli* bacteria cocultured with guinea pig RBC also yielded a similar type of switching to enhanced erythrocyte aggregation.

We propose the following hypothesis to explain the low-

energy SAW-mediated biofilm prevention phenomenon. Attraction or repulsion of bacteria in the 10-nm range near surfaces is an outcome of van der Waals and hydrophobic attraction forces being counteracted by electrostatic repulsion (6). This phenomenon known as the Z potential of the surface varies with the distance from the interface. SAW-induced elliptical vibrations affect the surface and are transmitted through the surrounding fluid media, causing the bacteria to vibrate with the same frequency. The amplitude of bacterial vibration is smaller than that of the surface, is governed by Stoke's law, and results in a relative velocity of bacteria respective to the surface (16). When the SAW-generated bacterial vibration amplitudes are smaller than the Z-potential repulsive zone, an overall net repulsion occurs, preventing bacterial attachment. This is the hallmark of SAW. Increasing the bacterial vibration amplitudes to values exceeding the Z-potential repulsion zone results in a net attraction force, promoting the adhesion of bacteria. Such SAW intensities also activate bacterial docking and force sensor activities, and this synergism can elicit the increased adhesion of bacteria which we noted at the higher SAW intensities.

The studies which show that SAW reduces biofilm bioburden on catheter segments in suspensions with several gram-negative and -positive bacteria as well as fungi indicate that the action of SAW is efficacious against a broad spectrum of microorganisms and not limited to selected groups. The studies in rabbits demonstrate the feasibility of delaying catheter-associated urinary tract infections with SAW. Conditioning films encrusted with proteins, electrolytes, and other organic molecules that develop on urinary catheters shortly after their insertion (23) do not appear to interfere with biofilm prevention by SAW. The absence of any detectable adverse effects from treatments with SAW suggest that this system may potentially be attached to a variety of indwelling medical devices, including endotracheal tubes and central venous or peritoneal dialysis catheters. The entire medical device industry, including prosthetic joints and others, is likely to benefit from this approach.

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Revision: 07/01/05

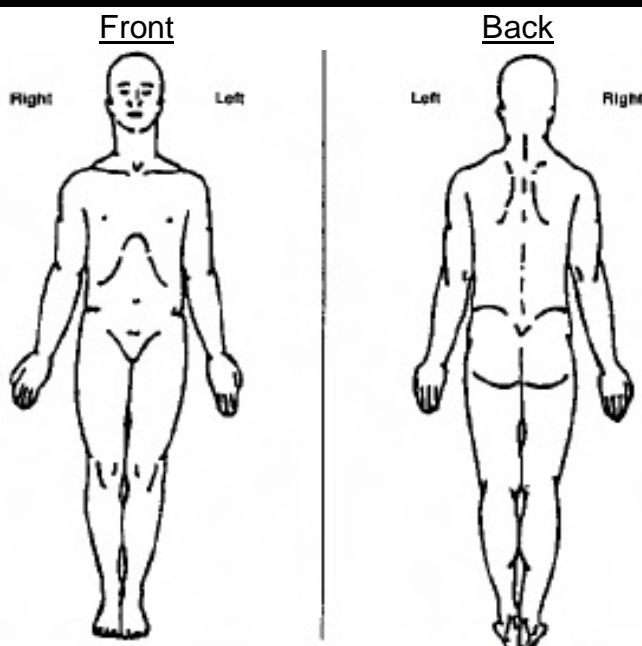
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Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average**.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain Pain As Bad As You Can Imagine



Subject's Initials : _____

Study Subject #:				
-------------------------	--	--	--	--

Study Name: _____

Protocol #: _____

PI:

Revision: 07/01/05

PLEASE USE
BLACK INK PEN

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

☐ No Relief ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Interfere Completely Interferes

B. Mood

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Interfere Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does Not Interfere Completely Interferes

E. Relations with other people

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Interfere Completely Interferes

F. Sleep

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Interfere Completely Interferes

G. Enjoyment of life

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Does Not Interfere Completely Interferes

רשימת כאב מצומצמת
(טופס מקוצר)



תאריך: _____ שעה: _____

שם משפחה: _____ שם פרטי: _____

1. לאורך ימי חיינו, לרובנו היה מידי פעם כאב (כמו כאבי ראש קלים, נקע, וכאבי שיניים) האם היה לך איזה שהוא כאב יום יומי אחר מאלו היום?

1. כן 2. לא

2. על הדיאגרמה, הצלל את האזורים במ אתה חש כאב. שים "X" על האזור הכואב ביותר.

			
--	---	--	--

3. נא לדרג את הכאב שלך על ידי סמון עיגול סביב המספר האחד המתאר ביותר את הכאב הגרוע ביותר שיש שלך ב-24 השעות האחרונות

10	9	8	7	6	5	4	3	2	1	0
										אין כאב
הכאב הגרוע ביותר שאתה יכול לדמיין										

4. נא לדרג את הכאב שלך, על ידי סמון עיגול סביב המספר האחד, המתאר ביותר את הכאב החלש ביותר שיש לך ב-24 השעות האחרונות

10	9	8	7	6	5	4	3	2	1	0
										אין כאב
הכאב הגרוע ביותר שאתה יכול לדמיין										

5. נא לדרג את הכאב שלך, על ידי סמון עיגול סביב המספר האחד, המתאר ביותר את הכאב הממוצע שיש לך.

10	9	8	7	6	5	4	3	2	1	0
										אין כאב
הכאב הגרוע ביותר שאתה יכול לדמיין										

6. נא לדרג את הכאב שיש לך על ידי סמון עיגול סביב המספר האחד המתאר עד כמה יש לך כאב ברגע זה.

10	9	8	7	6	5	4	3	2	1	0
הכאב הגרוע ביותר שאתה יכול לדמיין										אין כאב

7. איזה טיפול או תרופות הנך מקבל/ת נגד הכאב שלך?

8. במשך 24 השעות האחרונות, עד כמה הקלה סיפקו לך טפול בכאב או תרופות? אנא סמן את האחוזון האחד המראה ביותר עד כמה היתה לך הקלה.?

100%	90%	80%	70%	60%	50%	40%	30%	20%	10%	0%
הקלה מלאה										אין הקלה

9. סמן בעגול את המספר האחד המתאר איך, במשך 24 השעות האחרונות, הכאב הפריע לך ב:

א. פעילות כללית										
10	9	8	7	6	5	4	3	2	1	0
הפריע לחלוטין										לא הפריע
ב. מצב הרוח										
10	9	8	7	6	5	4	3	2	1	0
הפריע לחלוטין										לא הפריע
ג. יכולת הליכה										
10	9	8	7	6	5	4	3	2	1	0
הפריע לחלוטין										לא הפריע
ד. עבודה רגילה (כולל גם עבודה מחוץ לבית וגם עבודת בית)										
10	9	8	7	6	5	4	3	2	1	0
הפריע לחלוטין										לא הפריע
ה. יחסים עם אנשים אחרים										
10	9	8	7	6	5	4	3	2	1	0
הפריע לחלוטין										לא הפריע
ו. שינה										
10	9	8	7	6	5	4	3	2	1	0
הפריע לחלוטין										לא הפריע
ז. הנאות החיים										
10	9	8	7	6	5	4	3	2	1	0
הפריע לחלוטין										לא הפריע

שאלון SF-12

1. כיצד היית מעריך את מצב בריאותך באופן כללי בהשוואה לבני גילך?
 1. מצוין 2. טוב מאוד 3. טוב 4. סביר 5. גרוע

ביום טיפוס - איזה מידה מגביל אותך מצב בריאותך בביצוע הפעולות הבאות?

פעילויות	מגביל מאוד	מגביל מעט	לא מגביל כלל
2. פעילויות מתונות כמו: הזזת שולחן, שימוש בשואב אבק, פעילות ספורטיבית מתונה	1	2	3
3. עליה של מספר קומות במדרגות	1	2	3

בחודש האחרון במסגרת עבודתך או בפעילויות יומיומיות אחרות כתוצאה ממצב בריאותך הפיזי? (הקף ספרה אחת בכל שורה)

לא	כן	
2	1	4. האם ביצעת <u>פחות</u> משהיית רוצה?
2	1	5. האם היית <u>מוגבל/ת</u> בסוג עבודה או פעילויות אחרות?

בחודש האחרון במסגרת עבודתך או בפעילויות יומיומיות אחרות כתוצאה מבעיות רגשיות כלשהן (למשל הרגשת מדוכא/ת או חרד/ה)? (הקף ספרה אחת בכל שורה)

לא	כן	
2	1	6. האם ביצעת <u>פחות</u> משהיית רוצה?
2	1	7. האם לא עשית את עבודתך או פעילויות אחרות במידת <u>ההקפדה</u> הרגילה?

8. בחודש האחרון עד כמה הפריעו לך כאבים לביצוע עבודתך? (כולל עבודה מחוץ לבית ועבודות בית) (הקף בעיגול תשובה אחת)
 1. כלל לא 2. מעט 3. במידה מתונה 4. די הרבה 5. הרבה מאוד

במשך החודש האחרון כמה מהזמן (הקף ספרה אחת בכל שורה)

כלל לא	מעט מן הזמן	חלק מן הזמן	חלק ניכר מהזמן	רוב הזמן	כל הזמן	
6	5	4	3	2	1	9. הרגשת שלי/ה ורגוע/ה?
6	5	4	3	2	1	10. היית מלא/ה אנרגיה?
6	5	4	3	2	1	11. הרגשת מדוכא/ת ועצוב/ה

12. בחודש האחרון עד כמה הפריעו מצב בריאותך הפיסי או בעיותך הרגשיות לפעילויותיך

החברתיות (כמו לבקר חברים, קרובים) (הקף בעיגול תשובה אחת)

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Pain Disability Index

The Pain Disability Index is a tool designed to help patients measure the degree their daily lives are disrupted by chronic pain.

You can customize the form on the next page and add your practice name and address information in the area at the top of the page. Some forms include additional fields you can complete.

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Pain Disability Index¹

Name _____ Date _____

Pain disability index: The rating scales below are designed to measure the degree to which aspects of your life are disrupted by chronic pain. In other words, we would like to know how much your pain is preventing you from doing what you would normally do or from doing it as well as you normally would. Respond to each category by indicating the overall impact of pain in your life, not just when the pain is at its worst.

For each of the 7 categories of life activity listed, please circle the number on the scale that describes the level of disability you typically experience. **A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.**

Family/home responsibilities: This category refers to activities of the home or family. It includes chores or duties performed around the house (eg, yard work) and errands or favors for other family members (eg, driving the children to school).

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Recreation: This category includes hobbies, sports, and other similar leisure time activities.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Social activity: This category refers to activities that involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Occupation: This category refers to activities that are a part of or directly related to one's job. This includes nonpaying jobs as well, such as that of a housewife or volunteer worker.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Sexual behavior: This category refers to the frequency and quality of one's sex life.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Life-support activity: This category refers to basic life-supporting behaviors such as eating, sleeping, and breathing.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

References

1. Pollard CA. Preliminary validity study of the pain disability index. *Percept Mot Skills*. 1984;59(3):974.



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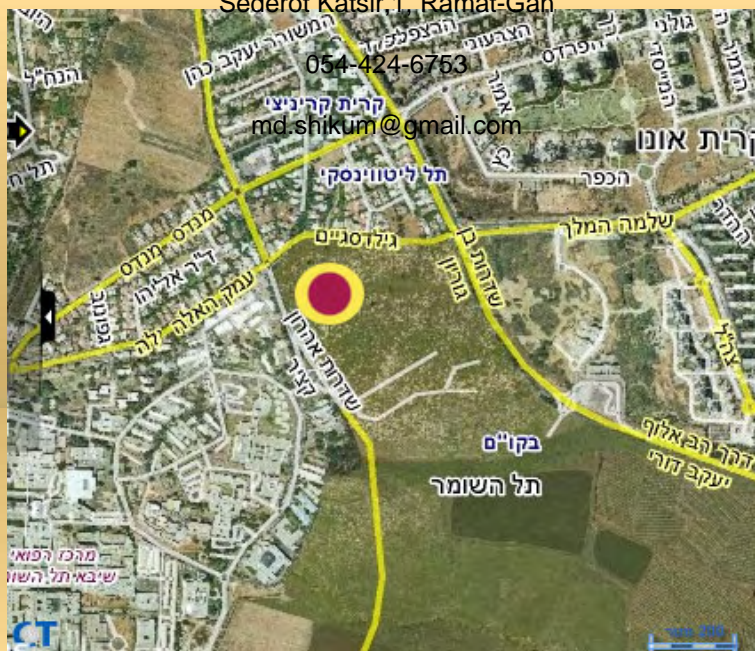
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Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery

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Object. Recent progress in the understanding of abnormal electrical behavior in injured sensory neurons motivated an examination, at the ultrastructural level, of trigeminal roots of patients with trigeminal neuralgia (TN).

Methods. In 12 patients biopsy specimens of trigeminal root were obtained during surgery for microvascular decompression. Pathological changes in tissue included axonopathy and axonal loss, demyelination, a range of less severe myelin abnormalities (dysmyelination), residual myelin debris, and the presence of excess collagen, including condensed collagen masses in two cases. Within zones of demyelination, groups of axons were often closely apposed without an intervening glial process. Pathological characteristics of nerve fibers were clearly graded with the degrees of root compression noted at operation. Pain also occurred, however, in some patients who did not appear to have a severe compressive injury.

Conclusions. Findings were consistent with the ignition hypothesis of TN. This model can be used to explain the major positive and negative symptoms of TN by axonopathy-induced changes in the electrical excitability of afferent axons in the trigeminal root and of neuronal somata in the trigeminal ganglion. The key pathophysiological changes include ectopic impulse discharge, spontaneous and triggered afterdischarge, and crossexcitation among neighboring afferents.

KEY WORDS • cranial nerve neuralgia • tic douloureux • trigeminal neuralgia • nerve pathophysiology • microvascular decompression

TRIGEMINAL neuralgia (tic douloureux) is a chronic pain syndrome characterized by brief, but excruciatingly intense stabbing or electrical shocklike pain paroxysms experienced in one or more divisions of the trigeminal distribution, either spontaneously or in response to gentle tactile stimulation of a trigger point on the face or in the oral cavity. Dandy¹⁶ and Gardner²⁹ proposed a causal relation between the pain paroxysms and compression of the trigeminal root by adjacent arterial loops or, occasionally, by tumors, arteriovenous malformations, or aneurysms. The hypothesis of microvascular compression was strongly supported by Jannetta^{37,38} and others, who documented not only that vascular contact occurs in a high proportion of patients with TN, but also that prolonged pain relief can often be obtained surgically by MVD.³⁰

These observations, as well as others, have led to the widely held opinion that the primary pathological factor in TN is demyelination of sensory axons due to sustained (static) or pulsatile microvascular compression of the trigeminal root.^{27,44} This idea also complements the fact that there is an increased incidence of TN in patients with multiple sclerosis^{36,63} and leads to the question, what is the link

between demyelination and pain paroxysms? Demyelination per se is expected to block impulse propagation, yielding numbness and not pain. In addition, activity in myelinated afferents is generally associated with innocuous touch and vibration sense.⁶⁷ Ephaptic contact between adjacent denuded axons has long been cited as a pain mechanism in TN,²² although little specific evidence of such coupling is actually available.⁴¹ Moreover, ephaptic contact should yield hyperesthesia by a one-to-one duplication (amplification) of afferent signals evoked by application of stimuli. It is not obvious how ephaptic contact could trigger pain paroxysms that outlast the trigger stimulus, or why the intensity of pain that is experienced is not proportional to the strength of the stimulus.⁴⁶ The aim of the present study was to bridge this explanatory gap by considering the lesion caused by microvascular compression in light of new information on the electrogenic properties of injured afferent axons.²⁰ A preliminary account was published previously.⁶¹

Clinical Material and Methods

Patient Population

Trigeminal root biopsy specimens were excised from 12 consecutive patients scheduled to undergo posterior fossa craniotomy and root exploration. The intention was to perform MVD and insertion of a shredded Teflon sponge

Abbreviations used in this paper: CNS = central nervous system; MVD = microvascular decompression; PNS = peripheral nervous system; TG = trigeminal ganglion; TN = trigeminal neuralgia.

wedge to maintain separation between the root and the compressing arterial or venous loop. The default procedure, to be performed if no compressing vessel was found, was a partial rhizotomy involving no more than one third of the root cross section. The rationale and predicted outcome of surgery was explained to the patients, including the intention to remove a small biopsy sample for investigational purposes. The patients were additionally informed that biopsy was unlikely to have significant positive or negative functional consequences beyond those of the surgery itself. Informed consent was obtained from all patients. These procedures were approved by the Helsinki Committees on Human Experimentation of the Rabin Medical Center and the Israel Ministry of Health.

Surgical Procedure

Clinical indications for surgery included typical idiopathic TN intractable to medical therapy. Surgery was offered to patients younger than 70 years of age without significant medical risks; others were encouraged to undergo a percutaneous rhizolytic procedure. All patients who underwent biopsy had undergone a regimen of anticonvulsant therapy including carbamazepine, phenytoin, and/or baclofen, with eventual recurrence of symptoms. One patient (Case 12) had previously undergone a neurolytic procedure involving retrogasserian injection of glycerol,³¹ and an additional three patients (Cases 7, 9, and 11) had undergone ablative surgery on peripheral branches of the trigeminal nerve. Individual patient parameters are summarized in Table 1.

After induction of general anesthesia, patients underwent surgery in the supine position with the head turned to the side opposite the site of pain. A linear retromastoid incision was followed by a 25-mm-wide craniectomy. At the junction of the transverse and sigmoid sinuses the dura mater was opened parallel to the sinuses. The superolateral aspect of the cerebellum was mobilized. An operating microscope was used for the intradural portion of the procedure. The arachnoid was opened over the trigeminal root, which was then inspected. Brain retraction was used sparingly until egress of cerebrospinal fluid allowed its discontinuation.

A convincing area of arterial compression was seen in seven of the 12 patients (Table 1). In three of these seven patients (Cases 1–3) there were grooves in and a grayish discoloration of the root at the site of contact, and in four of the patients (Cases 4–7) there were grooves in the rootlets or they were deformed by the vessel, but there was no obvious discoloration. In an eighth patient (Case 8), arterial contact was seen and minor compression was considered a possibility, although specific signs of this were absent. In these eight cases a biopsy sample was taken at the apparent site of injury (see later), and one or more shredded Teflon sponges were inserted between the trigeminal root and the offending vessel.

In four (Cases 9–12) of the 12 patients no arterial compression was detected, despite careful searching and, thus, partial rhizotomy was performed in the area of the root somatotopically appropriate to the symptomatology, to a depth of no more than one third of the root diameter. A biopsy sample was taken from the cut portion of the root. In two patients (Cases 9 and 10) prominent veins either coursed on the surface of the root or penetrated it, and in

one patient (Case 10) there was also possible arterial involvement. The veins were separated from the root, coagulated, and cut. In Case 12 we believed that there might have been an arterial conflict that resolved when the arachnoid was opened. In all three of these patients (Cases 9, 10, and 12) a Teflon sponge was inserted into the site. Finally, in Case 11 treatment was limited to partial rhizotomy because there was no hint of microvascular abnormality.

Biopsies, Control Tissue, and Histological Studies

The biopsy samples were 1 mm or less in diameter and approximately 4 mm in length. Using a diamond knife, a small incision was made into the trigeminal root sheath approximately 2 to 4 mm from the junction of the root and pons. A strand of nerve fibers was grasped with the aid of a microforceps and teased from the body of the root in the central-to-peripheral direction until a 3- to 4-mm strand was separated from the root. The peripheral end of the strand was then cut with microscissors. The resulting root biopsy sample was immediately removed and placed on a small sheet of dental impression wax. Ends were pinned to the wax under slight tension by using stainless steel minuten pins, and the wax sheet was immersed in a vial containing 1.5% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer (or occasionally PO_4 buffer), pH 7.4, at 20°C. The vial was then cooled to 4°C. The surgical procedure was completed in a routine manner.

During the course of this study we had the opportunity to examine a biopsy specimen from a patient with the diagnosis of glossopharyngeal neuralgia. Results are presented in a companion article.¹⁸ Additional comparison tissue was taken from animal and human sources to aid in the evaluation of possible artifacts. First, trigeminal root fragments were dissected from two rats (in which anesthesia had been induced by an intraperitoneal injection of 50 mg/kg pentobarbital) by using the same exposure, dissection, and fixation procedures used to obtain and prepare the human biopsy samples. Second, trimmed blocks of spinocranial root tissue and small fragments, teased similarly to the biopsy samples, were taken from three aldehyde-fixed human trigeminal roots obtained from cadavers (without known root disorders), and from the dorsal root end of two cervical and five lumbosacral dorsal root ganglia excised from live patients in the course of ganglionectomy for headache or for back and leg pain due to ruptured intervertebral disc, respectively. Additional trigeminal tissue was excised from a perfusion-fixed rat.

The fixed tissue samples were rinsed, immersed in 0.1 M cacodylate buffer containing 1.25% OsO_4 and 1.5% sodium ferricyanide (1–2 hours), dehydrated in ascending grades of ethanol, and embedded in resin. Semithin (1–2 μm) transverse or longitudinal sections stained with toluidine blue were used for orientation. Thin sections were cut from the middle of these blocks, laid on 300-mesh copper grids, stained with uranyl acetate and lead citrate, and examined with the aid of an electron microscope (JEOL 100CX; Japan Electron Optics Ltd., Akishima, Japan). Individual grid squares were located in relation to the whole specimen by matching the external boundary of the section and internal landmarks to the semithin sections. In two cases semithin sections were etched with saturated NaOH in ethanol, rinsed in ethanol, and air dried. They were then stained for

TABLE 1
*Patient characteristics and neuropathological findings**

Case No.	Age (yrs), Sex	Diagnosis	Pain Duration Preop (yrs)	Prior Treatment & Response	Surgical Findings	Lesion Severity†	Surgery	Pain Relief (follow up in mos)	Intact Axons at Specimen Edge	Pathological Findings†			
										Scattered Axons	Dysmyel	Excess Collagen	
1	57, M	lt V2 & 3 neuralgia	5	inadequate relief from CBZ	SCA loop compressing root anteriorly at pons exit w/ gray discoloration	+++	MVD	excellent (40)	yes	few	—	+++	+
2	60, M	rt V2 neuralgia	3	recently only partial response to CBZ	SCA loop made groove in inferior surface of root w/ discoloration, 4 mm from pons	+++	MVD	excellent (44)	no	yes	—	+++	—
3	59, F	lt V3 neuralgia	6	only partial response to 1000 mg CBZ	AICA loop compressing entire course of root w/ gray discoloration at contact site	+++	MVD	excellent (29)	no	yes	—	+++	+++
4	50, M	rt V2 neuralgia	5	lately receiving 2400 mg CBZ w/out benefit	2 branches of AICA made groove in inferior root surface 2–5 mm from pons	+++	MVD	excellent (49)	yes	yes	++	+++	+++
5	57, M	lt V2 & 3 neuralgia	2	no longer responds to drug therapy	root flattened between inferior & superior arterial loops	+++	MVD (both loops)	significant pain relief, small cerebellar infarct w/ unsteady gait (41)	no	yes	++	+++	++
6	61, M	lt V2 neuralgia	4	brief response to CBZ	large artery compressing anterior inferior aspect of root 2 mm from pons	++	MVD	excellent (50)	yes	yes	+++	+++	+++
7	66, F	lt V1 & 2 neuralgia	15	trigger-point alcohol injection, only partial response to CBZ	AICA loop compressing anterior root surface 2–4 mm from pons	++	MVD	excellent (34)	many‡	many‡	—	+	—
8	38, F	rt V2 & 3 neuralgia	3	only partial response to CBZ	2 small arteries contacting surface of root near pons, w/ clear compression	+	MVD	excellent for 35 mos, then pain recurrence, partial rhizot 56 mos after MVD yielded partial relief (59)	no	no	+	+++	+++
9	51, M	lt V1–3 neuralgia	6	stopped responding to multiple drugs, ION neurectomy 2 yrs preop	venous contact	+	excised veins, partial rhizot	excellent pain relief for 76 mos, recurrent V2 pain controlled by CBZ (78)	no	yes	++	+	—
10	45, M	rt V1–3 neuralgia	6	only partial response to CBZ	vein contacting root inferior surface, possible AICA contact on anterior surface	+	MVD of AICA, vein excised, partial rhizot posteriorly	excellent, partial numbness (27)	yes	yes	+	+	+
11	38, F	lt V3 neuralgia	5	poor response to drugs, ION neurectomy 4 yrs preop	no vascular compression or root contact seen	0	partial rhizot 3 mm from pons	significant pain relief but dysesthesias & numbness, receiving elatrol (69)	yes	yes	—	+	+
12	49, F	rt V2 & 3 neuralgia	5	glycerol rhizogangliolysis 5 mos preop, pain relief for 3 mos	possible AICA contact w/ inferior surface of root	+	MVD & partial rhizot	recurrent V2 pain at 54 mos postop, RF rhizolysis after 80 mos gave complete pain relief (12)	no	none	NA	NA	NA

* AICA = anterior inferior cerebellar artery; CBZ = carbamazepine; demyel = demyelination; dysmyel = dysmyelination; ION = infraorbital nerve; RF = radiofrequency; rhizot = rhizotomy; SCA = superior cerebellar artery.

† The symbols —, +, ++, and +++ indicate degrees of damage from none to severe.

‡ The site of biopsy was away from the site of compression.

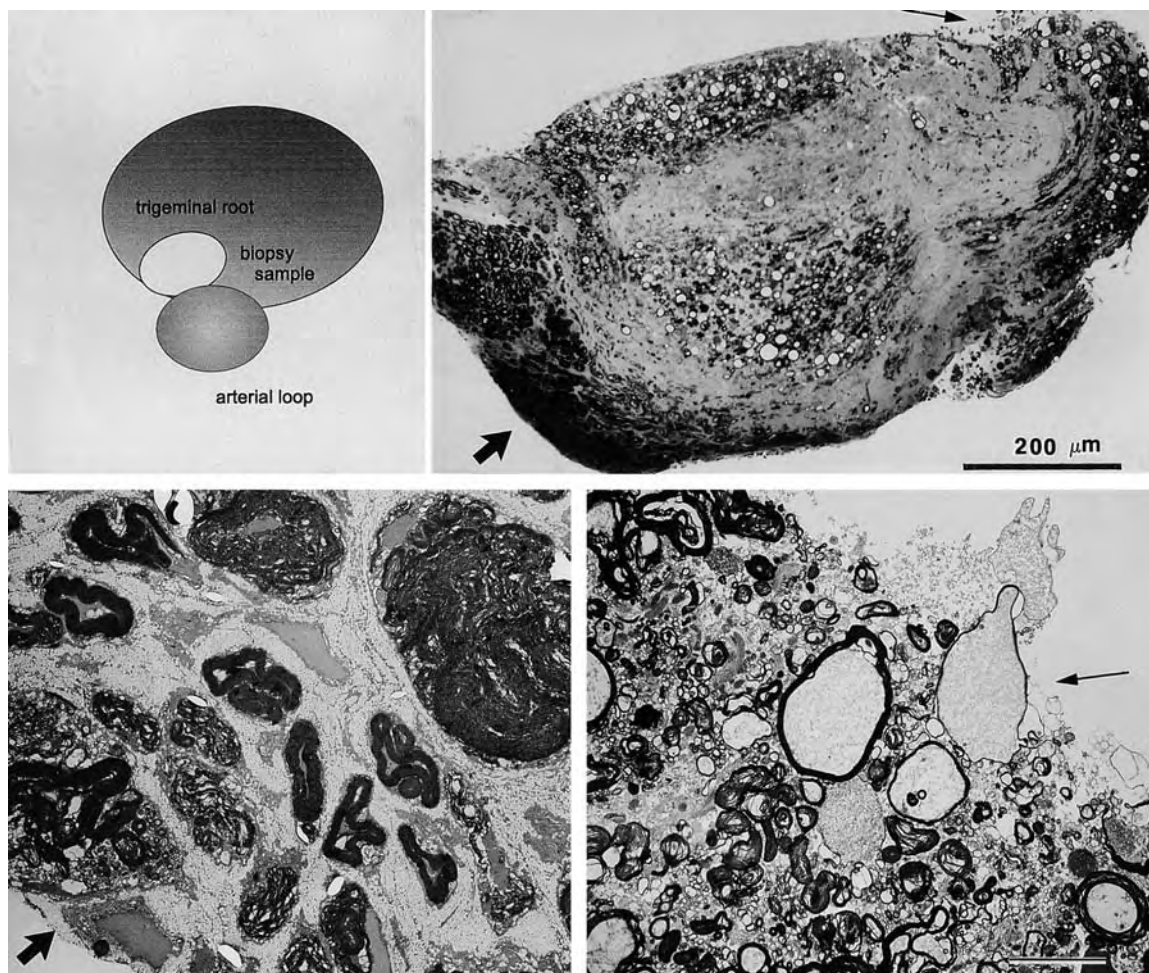


FIG. 1. Case 4. Documentation of pathological changes in the trigeminal root of a patient who underwent MVD surgery for relief of typical TN. *Upper:* Schematic representation of the relation of the biopsy sample to the trigeminal sensory root and compressing arterial loop (*left*) and light photomicrograph of the biopsy sample (*right*). *Lower:* Electron micrographs showing a zone of dysmyelination (*left*, note the plentiful collagen [white areas]) and a zone of demyelination (*right*) with abundant myelin debris. Arrows (*thick* and *thin*) indicate approximate locations represented in the electron micrographs. The *thick* arrow indicates the external (inferior) root surface that was adjacent to the compressing arterial loop. The *thin* arrow indicates the torn surface of the specimen, an area that was located in the interior of the root in situ. Bars: *upper*, 200 μ m; *lower*, 5 μ m.

collagen by using 0.5% aniline blue dye in saturated picric acid.⁴²

Histological data were evaluated by colleagues having no knowledge of the clinical status of the patient or whether the surgeon had identified any visible compression. All clinicopathological correlations were made post hoc.

Results

Orientation and Summary of Observations

Approximately one third to one half of the perimeter of each specimen was ragged, with unmistakable signs of having been torn from the subjacent root. The remainder had a natural root boundary (Fig. 1, *arrows*). This permitted orientation of the biopsy samples as they would have rested in situ and identification of the surface that contacted the compressing blood vessel, if any. Larger speci-

mens included a central region of severe injury and one or more edges that were relatively spared; smaller specimens showed axonal disruption throughout (Figs. 1 and 2).

The principal observation was massive disruption of tissue ultrastructure in the presence of microvascular root compression, with less damage in cases in which there was root contact without compression. There was a clear correspondence between the macroscopic appearance of the root during surgery and the microscopic observation of injury (Table 1). In areas of the most severe damage, few axons remained and nearly all that did were demyelinated. Adjacent areas contained more surviving axons, including a significant proportion having a residual myelin sheath, albeit disrupted. We refer to these areas as zones of "demyelination" and "dysmyelination," respectively. Histopathological findings always extended to at least one edge of the sample, and encompassed much of its cross section, implying that damage extended deeper into the trigeminal root,

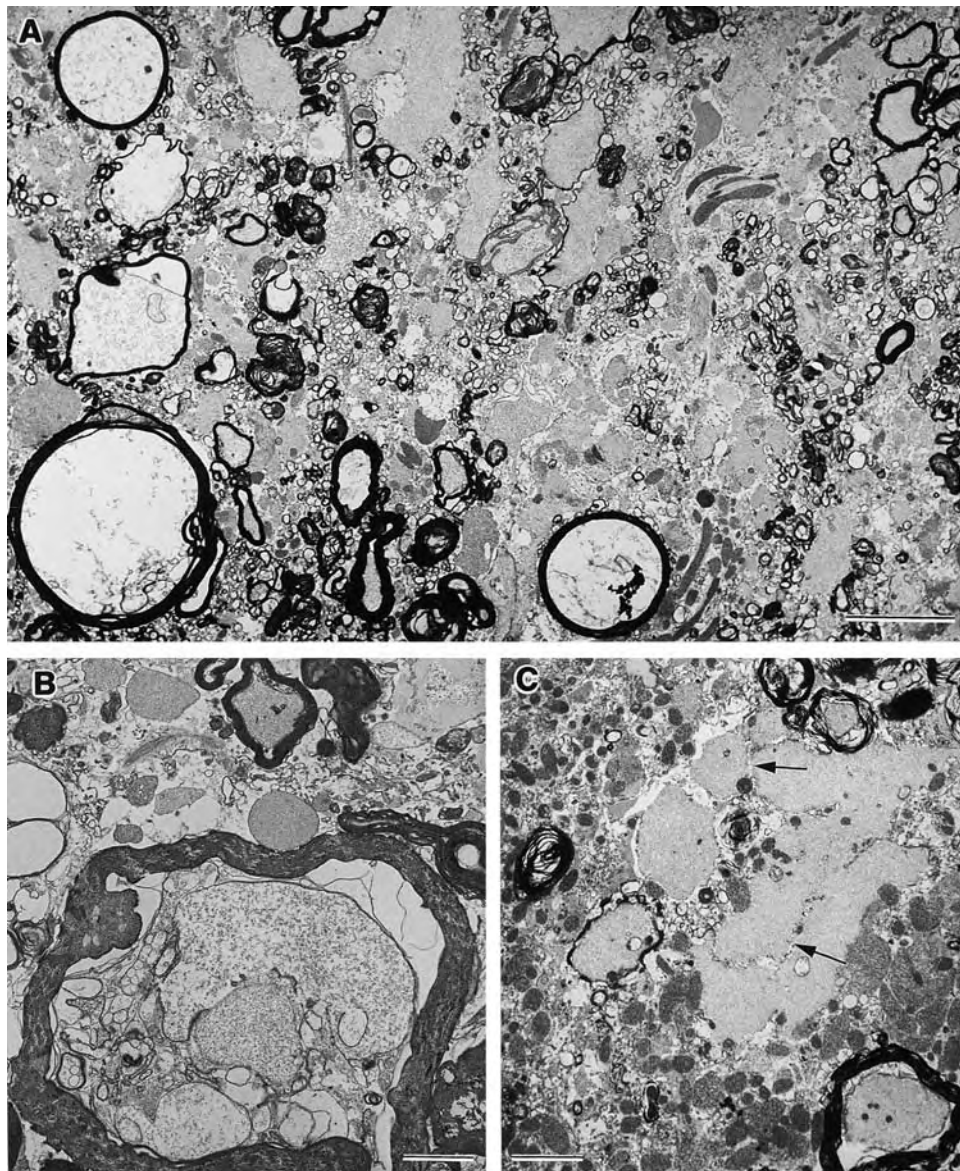


FIG. 2. Electron micrographs demonstrating tissue disorganization in trigeminal root biopsy samples. A: Case 4. Central zone of demyelination with residual myelin debris surrounded by dysmyelination. Note the swollen axons with thin compact myelin on the left. B: Case 5. Large myelin sheath containing numerous axon profiles of regenerating sprouts. C: Case 6. Cluster of demyelinated axons in close membrane-to-membrane contact (including where indicated by arrows). Many additional clusters of this sort are visible in A. Bars: A, 5 μ m; B and C, 2 μ m.

beyond the biopsy site itself. The most severe injury was not usually observed in a single contiguous region, but rather interdigitated with areas of less severe damage. Interestingly, the portion of sample perimeter directly apposed to the compressive blood vessel tended to be relatively spared (dysmyelinated; Fig. 1). There were no obvious signs of inflammatory infiltrates.

A peculiarity of many biopsy samples was a striking overproduction of collagen in the extracellular matrix (Table 1). Usually collagen fibrils filled the space between surviving axons diffusely. In two cases, however, there were massive clumps of nearly pure condensed collagen centered on a zone of severe demyelination and axon loss (Fig. 3). The makeup of the clumps was established using colla-

gen-specific staining and light microscopy, and was confirmed ultrastructurally by visualizing the characteristic periodic striations of collagen fibrils (Fig. 3E–G). The severe damage surrounding the clumps may indicate that they, in fact, contributed to the damage. Fibroblasts were present, but not in unusual density. An excess of collagen is a recognized sequel of compressive injury to spinal roots.²⁸

Areas of Axonal Loss and Demyelination

These regions were dominated by the following: 1) astrocytic processes; 2) a froth of single and multilamellar liposomes (0.2–1 μ m), residue of shattered myelin sheaths; and 3) large- and small-diameter axons mostly denuded of

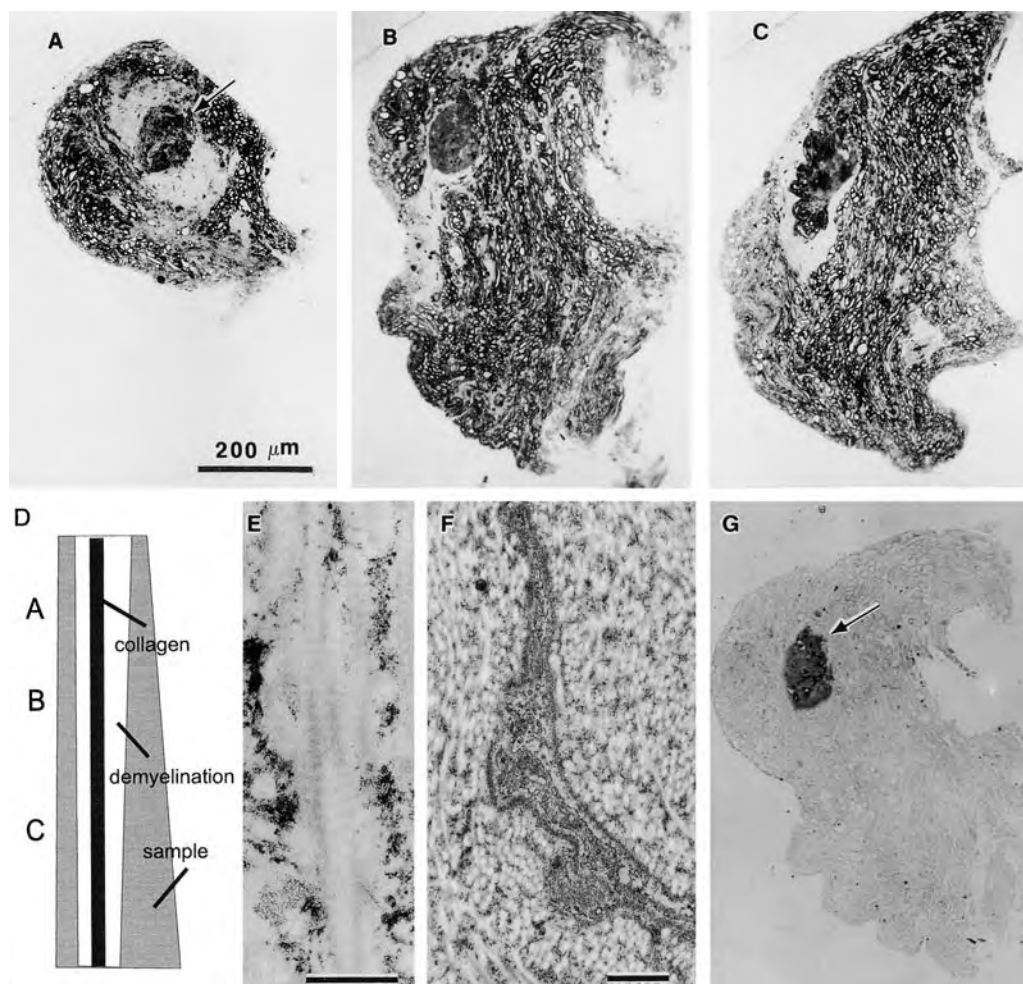


FIG. 3. A–C: Case 6. Photomicrographs of serial semithin sections from a trigeminal root biopsy sample in which a collagen mass was present (arrow) and surrounded by a zone of demyelination. D: Schematic reconstruction of the sample as it would appear in situ. Letters A–C indicate the approximate locations of the areas shown in the three corresponding photomicrographs. E–G: Electron micrographs (E and F) and photomicrograph (G) documenting that the mass consisted of nearly pure collagen. A longitudinal view of a collagen fibril within the mass, showing characteristic collagen striations (E); collagen fibrils in cross section (F); and a semithin tissue section stained for collagen (G). Bars: A–C and G, 200 μ m; E and F, 0.5 μ m.

myelin, with their axolemma directly exposed to the extracellular medium (Fig. 2). Axons were identified as demyelinated by virtue of a cross-sectional diameter in the range of 1 to 4 μ m. Small-diameter (< 1 μ m) nonmyelinated axons were also present, although they were not bundled by glial processes. Astrocytic and axonal profiles in human trigeminal roots were distinguishable on the basis of cytoplasmic structure, as demonstrated by electron microscopy immunolabeling for glial fibrillary acidic protein.³⁵

Denuded axons, in isolation and also in bundles, occurred in direct apposition to one another without an intervening sheet of glial cytoplasm (Fig. 2A and C). The axoplasm looked viable, and these axons did not appear to be degenerating. The density of axons was often much lower than that observed in contiguous dysmyelinated regions and, sometimes, there were no axons at all, evidence of massive axonal loss. Conspicuous by their absence were phagocytosing macrophages, cells that are highly prominent in comparable regions of injured peripheral nerves.^{25,26}

^{54,55} We do not know if this is a peculiarity of the trigeminal root or if phagocytes were present early and then withdrew. Be that as it may, considerable amounts of residual myelin debris remained (Figs. 1 and 2).

Areas of Dysmyelination

There were four main types of fiber injuries short of frank demyelination and axonal loss. The most striking dysmyelinated fibers had large (up to 40 μ m) round profiles, with a myelin sheath that was thin in proportion to the fiber diameter (Figs. 1 and 2A), apparently the result of swelling. The axonal cytoskeleton was fragmented within a watery matrix. A second form featured bulges and crenulated invaginations of compact myelin, with swelling of the glial cytoplasm present within the innermost loop(s) of myelin (the inner mesaxon), or within the compact myelin itself (presumably at Schmidt–Lanterman incisures). These changes were at the expense of a reduced axonal cross

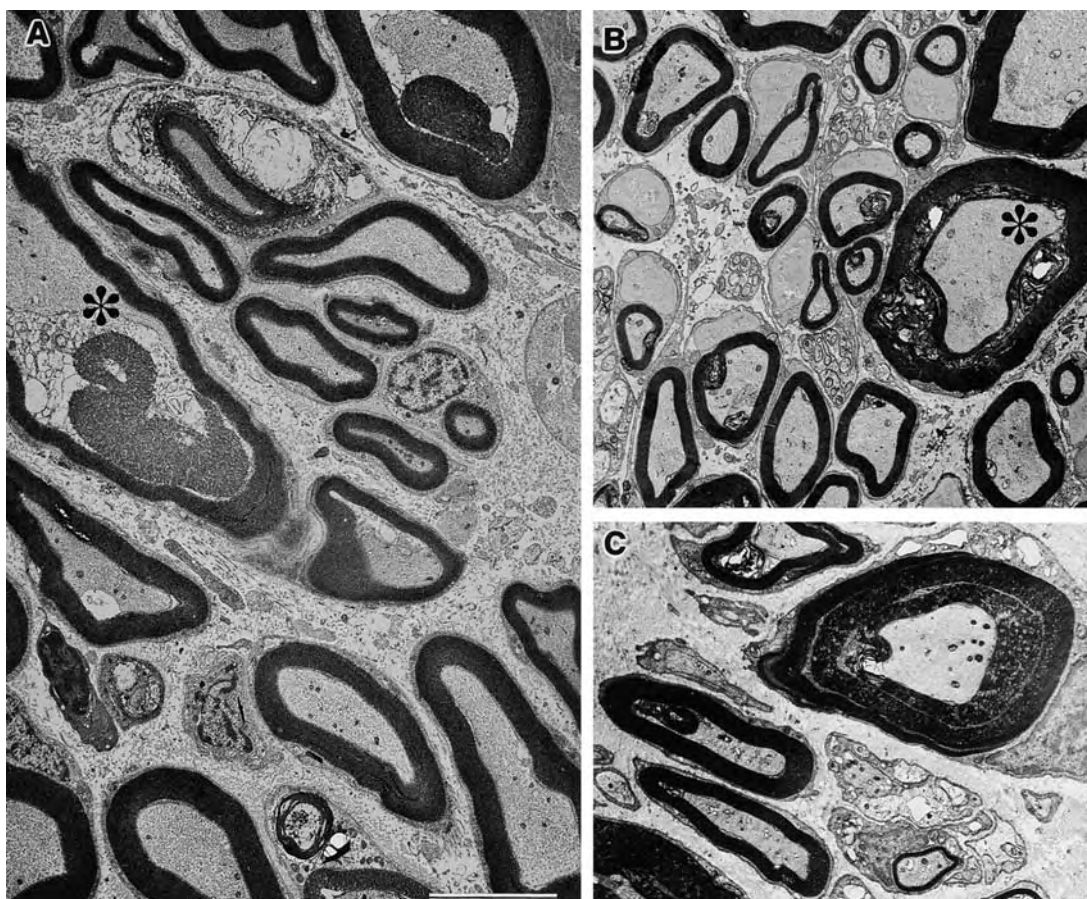


FIG. 4. Electron micrographs demonstrating relatively intact tissue to provide a comparison for regions of trigeminal root compression. A: Case 6. Spared edge of a trigeminal root biopsy sample. There was heavy de- and dysmyelination located more centrally in this sample (Figs. 2C and 3C). Most axons are relatively intact, but in some there is expansion of the inner (*asterisk*) or outer (upper left) mesaxon, or myelin invagination (upper right). B: Trigeminal root biopsy sample from a healthy rat. This sample was dissected and fixed by immersion just like the human trigeminal biopsy samples. Most axons are intact, but at least one (*asterisk*) shows cytoplasmic expansion within the compact myelin (presumably at an incisure), and several show minor delamination and myelin invaginations. C: Sample of a C-2 dorsal root from a patient who underwent C-2 ganglionectomy for the treatment of intractable headache. Bar: 5 μ m (for all images).

section (Fig. 1). A third form involved atrophy and loss of the ensheathed axon. The myelin lamellae loosened, interlamellar spaces opened (myelin delamination), and unraveled myelin lamellae came to fill the entire cross section of the nerve fiber (Figs. 1 and 2C).³⁴ In the past, this type of change has been interpreted as “hypermyelination” or “myelin proliferation.”^{9,41} Finally, a few fibers contained numerous (sometimes tens of) individual small and large axonal profiles, apparently regenerating sprouts, within an original, surviving myelin sheath. Neighboring profiles within a cluster were in close apposition (Fig. 2B). Sprouts presumably originated at the cut end of the parent axon, somewhere between the TG and the point of observation, although some may have been sprouts of adjacent axons that entered the myelin tube upstream.

Relatively Preserved Axons

Zones of dysmyelination often transitioned into areas where an increasing proportion of fibers were relatively well preserved (Figs. 1, 3, and 4A). Here we also began to

find bundles of unmyelinated afferents with a normal appearance (Remak bundles); however, there were always some dysmyelinated axons, particularly those of the crenulated type of myelin, representing 5 to 20% of the fibers present. Most specimens contained adjacent patches of fibers bearing both PNS and CNS types of myelin. This is consistent with the fact that samples had been taken from a site within a few millimeters of the point of root entry into the brainstem.¹⁰ Both types of myelin showed demyelinating and dysmyelinating injuries.

Although relatively preserved, axons in these areas had a higher proportion of myelin anomalies than axons taken from healthy young animals (Fig. 4B). Nevertheless, they were similar to our other control samples (see data given later) and to control samples studied by others.^{28,39,41,56} It is likely, therefore, that much of the residual abnormality in areas of relatively preserved tissue represents normal changes associated with aging, or artifacts of tissue preservation, rather than a pathological change associated with microvascular compression (see *Discussion*). The PNS type of myelin was better preserved than the CNS type in

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both biopsy and control samples. This may reflect differential susceptibility to microvascular compression.

Correlation with Observations at Surgery

Tissue was coded for the degree and type of microscopic injury, and only later was compared with macroscopic observations made at the time of surgery. Overall, the correlation was what might have been expected (Table 1). Cases in which root compression, flattening, or grooving were noted by the surgeon showed extensive dysmyelination, demyelination, and axon loss, with particularly severe damage found in cases in which discoloration was noted (especially in Case 1). Cases in which vessel contact alone was noted had less damage, mostly dysmyelination rather than demyelination, and more preserved axons. Damage was similar whether microvascular compression affected the superior or the inferior surface of the root. In the one case in which there was no hint of microvascular abnormality (Case 11), there was no evidence of demyelination, only modest dysmyelination, and many axons that appeared intact. Hilton, et al.,³⁵ likewise reported minimal pathological findings in five TN biopsy samples in which no microvascular compression could be documented at the time of surgery.

In the patient in whom the most severe tissue necrosis was found (no surviving axons evident, Case 12), microvascular compression was minor at best. On decoding, however, we found that this patient had undergone glycerol rhizogangliolysis 5 months preoperatively. It is unlikely that the entire trigeminal root had been killed by the glycerol because the patient did not experience dense numbness before surgery and still had some sensation after partial rhizotomy. Perhaps necrosis was heaviest on the root surface from where the biopsy sample was taken.

All patients had experienced severe pain preoperatively, severe enough to warrant intracranial surgery. We believed that it was futile and ultimately misleading to try to quantify the relative severity of preoperative pain and we do not know, therefore, whether the extent of root injury correlated with the severity of the patients' symptoms. Qualitatively, the clinical presentation of patients who ultimately proved to have had clear microvascular compression and corresponding histopathological findings was no different from those who had minor or no vascular contact and a relatively preserved root structure. Finally, there was no obvious relationship between the spatial extent of pain (that is, pain in one, two, or three trigeminal divisions) and the degree of injury subjacent to the offending blood vessel (Table 1).

Control Tissue

The degree and type of axonal injury in biopsy samples is best appreciated by a comparison with control tissue. Although the contrast is most stark when compared with tissue taken from a healthy young animal that had been fixed optimally by vascular perfusion, even in this material occasional fibers (especially those with the CNS type of myelin) displayed some myelin crenulation and delamination. Dysmyelination occurred in a larger proportion of fibers taken from fixed human cervical root samples (all having the PNS type of myelin; Fig. 4C). Interestingly, tissue from patients with intervertebral disc herniation was very simi-

lar. Either the herniation in these cases occurred away from the location where the tissue was taken, or disc herniation (which is extradural) triggers relatively modest neuropathological conditions.

A serendipitous opportunity to observe essentially normal human trigeminal root was provided by the patient in Case 7. In this one patient, root compression was recorded at surgery, but only minor dysmyelinating changes were observed histologically. A retrospective check of the surgical notes in this case revealed that the presence of a collateral artery precluded obtaining a biopsy specimen in the center of the area of microvascular compression and, thus, the sample was taken just laterally, no more than 1 mm from the main site of compression. Similarly, in the case of glossopharyngeal neuralgia that we examined,¹⁸ intact fascicles were located closely adjacent to damaged ones. The images shown in Fig. 4A and C, therefore, reflect the normal state of craniospinal root tissue, including normal changes brought about by aging and artifacts caused by our tissue fixation protocol. Correspondingly, the changes shown in Figs. 1 through 3 reflect veridical effects of microvascular compression.

Finally, certain changes seen at the torn edge of the biopsy specimens can be attributed to a mechanical (dissection) artifact rather than a compression injury, on the grounds that similar changes occurred in control tissue. This includes fibers in which myelin was wrenched off the axon, leaving either partly exposed axolemma or torn axons with extruded axoplasm (for example, Fig. 1, *thin arrow*). Interestingly, some torn myelin lamellae in the control tissue had already formed closed bubbles (liposome-like froth) during the few seconds between sample dissection and fixation. Control samples torn (teased) off roots that had already undergone fixation, both in human and rat material, displayed certain artifacts not observed in biopsy samples such as myelin lamellae that were split and stretched into a form resembling a spider's web. These and other gross processing artifacts rendered this material unsuitable for comparative purposes.

Discussion

Trigeminal Root Injury in TN

Massive injury to nerve fibers was found in the trigeminal root subjacent to sites of microvascular compression in patients with TN, and its severity was clearly graded with the degree of compression noted by the surgeon during the operation. In several patients, however, vascular contact was minor and injury minimal. We are aware of only one earlier case report on TN in which compression damage to the trigeminal root was documented in material obtained intraoperatively.³⁵ Massive pathological changes were observed, which are consistent with our observations. In that study the authors also noted several additional cases of typical TN in which no microvascular involvement and no root lesion was found. Together, these observations strongly support the contention that microvascular compression can damage trigeminal root fibers in patients with TN, and they define the nature of the lesion. Major challenges posed by the data are the need to account for TN pain in those patients in whom root compression and axonopathy are minimal and to explain the distinctive pain symptomatology

observed in patients with TN in terms of axonopathy when it is present (see introductory remarks).

For obvious reasons we could not excise and examine portions of the trigeminal root that were expected to be healthy. Nonetheless, our data support the conclusion that root damage was focal, directly related to vascular contact, and in line with the degree of compression and discoloration seen during surgery. First, the larger samples all had areas of relatively intact axons adjacent to the zone of injury, indicating that the biopsy extended slightly beyond the area of severe injury. Assuming that most samples were taken roughly from the center of the area of vascular contact, as intended, the main area of damage would have been only 1 to 2 mm across, involving no more than approximately one quarter of the root in most cases. Second, data obtained in Case 7 revealed that axons were mostly intact at positions only marginally set off from the site of microvascular contact. The focal nature of the root injury is also consistent with the localized distribution of pain in TN. Likewise, it explains the relatively small changes in trigeminal somatosensory evoked potentials in patients with TN,⁴⁷ and their limited sensory deficit.⁵⁹

Our observations are generally consistent with those in many earlier reports of ultrastructural change following mechanical injury (including compression) to peripheral nerves and spinal/cranial roots.^{9,23,24,41,48,51,54,55} The myelin sheath is particularly sensitive and undergoes graded changes from minor dysmyelination to frank disintegration as trauma becomes more severe. One peculiarity of the trigeminal root material was the apparently inefficient removal of myelin debris. In addition to myelin damage, there was clear axonal loss in the most severely affected parts of the root. Interestingly, there were equally prominent signs of axonal sprouting, confirming that the sensory cell soma in the TG survives axotomy.

Two detailed neuropathological studies are available on excised TGs and closely adjacent parts of the trigeminal nerve and sensory root in patients who underwent surgery for TN. This work was carried out in the early days of electron microscopy, a period when ganglionectomy was still used in the management of TN.^{8,9,40,41} Although it was not stated explicitly by the authors, it is unlikely that the specimens examined included the portion of root located near the pons, where microvascular compression is most commonly observed. Both studies revealed considerable pathological changes, notably dysmyelination, some frank demyelination, and some axonal loss. Such changes were seen in essentially all patients suffering from TN, including those who had not undergone any previous neurolytic procedure. The authors were well aware of the need to factor in processing artifacts and normal aging changes unrelated to TN pain. Pathological changes were more prevalent in patients with TN than in controls (age-matched postmortem material), although even in patients the pathological conditions were much less massive than those found in our material; for example, Kerr and Miller⁴¹ typically needed to scan three to four tissue blocks to reveal convincing changes (see discussion on p 312 of that study).

Root Disease and Pain

According to Beaver,^{8,9} Kerr,^{40,41} and their colleagues, nearly all patients with TN had significant TG injury. In

the light of current knowledge, however, a significant proportion of these patients must also have had a compression injury at the trigeminal root. This was not reported, presumably because the proximal root is not exposed for ganglionectomy and was, therefore, not available for histological analysis. For the same reason, we did not have access to TG tissue from our patients. Had we examined the TG in our patients, no doubt we also would have observed pathological changes. Indeed, root compression itself probably causes retrograde changes in the TG, although the reverse is not the case. In patients with primary damage to the TG one would not see what we observed of focal root injury restricted to a zone immediately subjacent to a compressing blood vessel. Rather, in these patients one would have observed intact roots (if the TG injury were primarily demyelinating) or anterograde (wallerian) degeneration with axonal loss (if TG somata or axons had been killed).

In the absence of quantitative data on pain intensity we cannot comment on the possible correlation between degrees of injury and pain. In several patients, however, there was minimal overt injury, but enough pain to justify a major neurosurgical procedure. Hilton, et al.,³⁵ also reported five such cases. We propose two possible explanations. First, in some individuals, minimal root injury may be enough to yield significant pain.^{19,53} Second, and more likely, patients with TN without root injury may be ones in whom the primary disorder is located in or near the TG. For patients with a primary root compression lesion, MVD is the treatment of choice, although other options are also viable. For patients with TN whose primary lesion is located in the TG, partial rhizotomy is a rational default procedure. Either way, the pain mechanism is probably the same. As discussed later, the specific afferent pathophysiological characteristics that we believe underlie TN pain are expressed both in axons of the trigeminal root and in axons and neuronal somata of the ganglion.^{20,60,68,70}

Adams¹ has argued that microvascular contact with trigeminal roots and root injury do not specifically cause TN, but rather reflect normal changes related to aging. Our patients were relatively young (53 ± 9 years of age), histopathological changes were observed in all patients with microvascular contact, and the degree of injury was graded with the degree of compression. Moreover, severe changes were restricted to the quadrant of the root that directly abutted the offending vessel. Finally, microvascular compression (as distinct from mere vascular contact) appears to be common in patients with TN and rare in individuals without TN.^{32,33,52,65} We conclude that damage caused by trigeminal root compression is a sufficient condition to induce symptoms of TN, although it is not a necessary condition.

Mechanism of Pain Paroxysms in TN: the Ignition Hypothesis

Assuming that root and/or TG lesions are, indeed, the usual cause of TN, how do they induce the characteristic symptomatology of TN? An answer is provided by the ignition hypothesis.⁶⁰ The key is the discovery that sensory neurons frequently become electrically hyperexcitable when injured and a source of abnormal spike discharge.^{11,20,43,68,70} In cases of TN, such ectopic pacemaker activity could arise in the following: 1) dys- or demyelinated root ax-

ons; 2) swollen endbulbs and sprouts at the end of severed axons; and 3) axotomized cell somata within the TG. When ectopic firing occurs spontaneously, as it frequently does,²⁰ it presumably gives rise to background paresthesias and burning sensations, as reported by some patients with TN.^{27,30} Other injured sensory neurons are silent, but have a hair-trigger threshold such that momentary stimulation induces a burst of spontaneous firing lasting for seconds or even minutes. This triggered activity, or neuronal afterdischarge,^{6,20,49} is proposed in the ignition hypothesis to be the cause of the pain paroxysms associated with TN. Although afterdischarge is set off by an external stimulus, the spiking itself is self sustaining, a reflection of the intrinsic repetitive firing tendency of injured afferent neurons.^{6,7,20} Afterdischarge bursts may also occur without any obvious trigger stimulus.

As long as neurons with ectopic afterdischarge fire independently, the sensation they evoke is expected to resemble a prolongation of the sensation normally evoked by the trigger stimulus. The intense paroxysms of pain experienced by patients with TN and their sudden onset indicate that something must be synchronizing the afterdischarge bursts in large numbers of TG neurons. The ignition hypothesis proposes that synchronization of afterdischarge is a result of neuron-to-neuron crossexcitation⁶⁰ at the site of root compression or in the TG. Two well-established processes probably contribute to the synchronization: ephaptic crosstalk and "crossed afterdischarge."²⁰

One of the striking observations in our biopsy material and in that of Hilton, et al.,³⁵ were groups of axonal profiles devoid of myelin sheaths, in close apposition to one another without an intervening glial process. Close membrane apposition is a pathological condition known to facilitate axon-to-axon crossexcitation.^{2,17,24,45,50,62,64} Thus, momentary stimulation of a facial or intraoral trigger point innervated by one or more members of such a coupled group might activate the entire group, resulting in a pain paroxysm.

The second synchronizing mechanism, crossed afterdischarge, is probably even more important for TN paroxysms because it affects a much larger proportion of afferent neurons. Crossed afterdischarge is a newly discovered form of nonsynaptic, nonephaptic coupling that occurs both within sensory ganglia and at sites of nerve injury. Specifically, impulse activity evokes nonsynaptic release of a neurotransmitter(s) and/or K⁺ ions into the interstitial space. These mediators move by diffusion and excite intrinsic burst activity (afterdischarge) in neighboring neurons.^{3,4,21,49,57,66} As is the case with ephaptic crosstalk, a brief stimulus at a peripheral trigger point could be enough to evoke a massive synchronous afterdischarge by this mechanism.⁶⁰

According to the ignition hypothesis, the effects of both synchronizing mechanisms may be augmented by positive feedback; that is, each new neuron recruited following the initial trigger stimulus tends to recruit activity in additional neighboring neurons. These, in turn, elicit activity in still more neurons. The resulting chain reaction is felt as a paroxysmal explosion, the characteristic lightning attack of TN.⁶⁰ It should be noted that crossed afterdischarge is preferentially triggered by activity in A β afferents, those that are activated by light touch.^{4,21} Correspondingly, pain paroxysms in TN are typically triggered by light touch stimuli and not by pinch.^{13,46} Moreover, both ephaptic contact and crossed afterdischarge support the spread of activity from

A β touch afferents to nociceptors.^{4,24} Such spread is presumably what renders TN paroxysms painful. Central sensitization is unlikely to play a major role in TN because tactile allodynia and hyperalgesia are not usual symptoms.⁴⁴

Finally, one wants to account for the characteristic electrical shocklike quality of pain paroxysms in TN. Everyday electrical shocks evoke high-frequency (50 or 60 Hz) activity in all types of afferents simultaneously. This is the neural activity that gives rise to the shocklike sensation. Paroxysms of ectopic afterdischarge, amplified and synchronized by ephaptic crosstalk and crossed afterdischarge, are expected to evoke just this pattern of activity.

Self-sustaining afterdischarge in sensory neurons does not usually persist for more than a few tens of seconds. The mechanism that stops the burst is hyperpolarization due to a Ca⁺⁺-activated K⁺ conductance activated by Ca⁺⁺ entry during the burst.⁵ The burst-triggered hyperpolarization, which may last for several minutes, also renders the cell less responsive than normal to subsequent trigger stimuli. This is the proposed explanation of the refractory period that occurs in TN, the observation that following an attack a second attack cannot be triggered until 2 to 3 minutes have passed.⁴⁶ The hair-trigger nature of paroxysmal bursts may also account for the sometimes prolonged remissions that are a characteristic of TN. Long-term processes such as partial remyelination, or normalization of membrane channel marshaling,²⁰ may bring the triggering level below threshold for long periods of time.

Treatment Modalities in Light of the Ignition Hypothesis

The ignition hypothesis accounts for the major positive and negative signs and symptoms of TN, and for its pathogenesis following microvascular root compression.⁶⁰ The same neuronal changes (ectopic hyperexcitability, afterdischarge, and crossexcitation) are also known to develop in sensory ganglia following either axotomy or direct trauma to the ganglion.^{20,68,70} The ignition hypothesis, therefore, works equally well for cases in which there is no microvascular root compression but there is a TG lesion.⁶⁰ In the case of root compression, ignition may be exacerbated by the pounding of the arterial loop on the compression site, a region known to be abnormally mechanosensitive.¹⁵ The cardiac rhythm expected by this pounding is presumably obscured by the long time constant imposed by neuronal afterdischarge. Removal of the vessel by MVD surgery provides immediate relief; long-term relief presumably results from root recovery, primarily due to remyelination.

The ignition hypothesis also accounts for the effectiveness of medical treatment. Anticonvulsant medications such as carbamazepine, phenytoin, and lamotrigine are membrane stabilizers (Na⁺ channel blockers) that suppress ectopic neural firing.^{12,14,20,69} This action occurs in the PNS, over and above the role these agents play in suppressing seizure activity in the CNS. As the lesion progresses, ever increasing doses of these drugs are required until CNS side effects such as nausea and sedation become intolerable and surgical intervention is required. Membrane stabilizing drugs that are excluded from the CNS might prove an alternative therapeutic strategy.

A key prediction of the ignition hypothesis that distinguishes it from hypotheses based on a CNS cause²⁷ is the presence of paroxysmal discharge in primary afferent neu-

rons serving areas of the face to which pain is referred. This prediction might be verified by referral to microneurographic recordings from peripheral nerve branches. Another approach is to detect effector consequences of antidromic activity in peripheral nerves, such as neurogenic inflammation. Indeed, Nurmikko and associates⁵⁸ recently reported finding cutaneous vasodilation in patients with TN during paroxysmal attacks with the aid of laser-Doppler flowmetry. Verification of the ignition hypothesis is not merely of academic interest, but it suggests specific new avenues for the development of novel treatment modalities.²⁰

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Recovery of nerve conduction following microvascular decompression for trigeminal neuralgia

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Article abstract—*Objective:* To assess the function of trigeminal nerve before and after microvascular decompression for trigeminal neuralgia. *Background:* To date there is no direct evidence that microvascular decompression of the trigeminal root restores normal conduction in the nerve. *Methods:* The authors examined 10 patients with trigeminal neuralgia in whom preoperative MRI and MR angiography demonstrated neurovascular contact. During microvascular decompression, the trigeminal nerve was monitored by recording early scalp trigeminal evoked potentials immediately before, during, and after decompression. Direct recordings from the root entry zone were also performed. *Results:* In all patients preoperative scalp evoked potentials showed impaired conduction of the trigeminal root. Microvascular decompression was associated with immediate recovery of conduction in seven patients, demonstrated by both scalp evoked potentials and direct root recordings. All 10 patients were pain free postoperatively. *Conclusions:* Improvement in trigeminal neuralgia following microvascular decompression is often associated with normalization of neurophysiologic data, suggesting recovery of nerve function. Rapid electrophysiologic recovery and pain relief following microvascular decompression argue that neither phenomenon is linked to remyelination. It is possible that the trigeminal evoked potentials might predict an effective microvascular decompression.

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Anatomic, surgical,^{1–3} and neuroimaging studies⁴ lend support to the hypothesis that vascular compression or contact with the trigeminal nerve at the root entry zone is a major factor in the pathogenesis of “tic douloureux,” even if it is not the only factor responsible. This has led to microvascular decompression being widely used. Furthermore, microvascular decompression does not produce the neurologic deficit⁵ seen with ablative techniques. Pain is almost always relieved immediately after the operation.^{6,7} Although relief of the nerve from vascular contact appears to be an obvious mechanism for microvascular decompression, it has also been argued that the benefits may be the result of subclinical damage to the nerve during the operative dissection.⁸ This view has been challenged on the basis that subtle sensory deficits found preoperatively disappear after microvascular decompression.⁹ Owing to the small magnitude of these changes, they cannot be demonstrated in individual patients, but rely on statistical methods applied to a population of patients.⁹ Because, by definition, “essential” trigeminal neuralgia offers no clinical signs other than its characteristic symptom—particularly severe shooting pain—the question as to whether the relief of pain is linked to a normalization of the nerve function at the root entry

zone by microvascular decompression has been unable to be tested. Electrophysiologic testing of the trigeminal afferents can now be performed with a high degree of accuracy, reproducibility, and sensitivity by means of the trigeminal evoked potentials.¹⁰ After stimulation of the infraorbital nerve, recordings of scalp electrical responses¹¹ represent the far-field reflection of the incoming volley passing through high-medium velocity fibers just before the Gasserian ganglion (component W1), the retro-Gasserian root (component W2), and inside the brainstem, just after the entry zone (component W3).¹² Using these techniques, approximately 50% of patients with trigeminal neuralgia, in the absence of clinical signs or symptoms, have alteration of the afferent conduction, mainly localized at the root entry zone.¹³ Such findings are in agreement with the results reported regarding alteration of quantitative sensory testing in the same type of patients.^{14,15} Thus trigeminal evoked potentials are an instrument to test the hypothesis that function is made normal by microvascular decompression. During the operation, the trigeminal nerve is exposed at the pons—the site of the root entry zone—and this provides an opportunity to make recordings directly from the root and is another tool to test this hypothesis.

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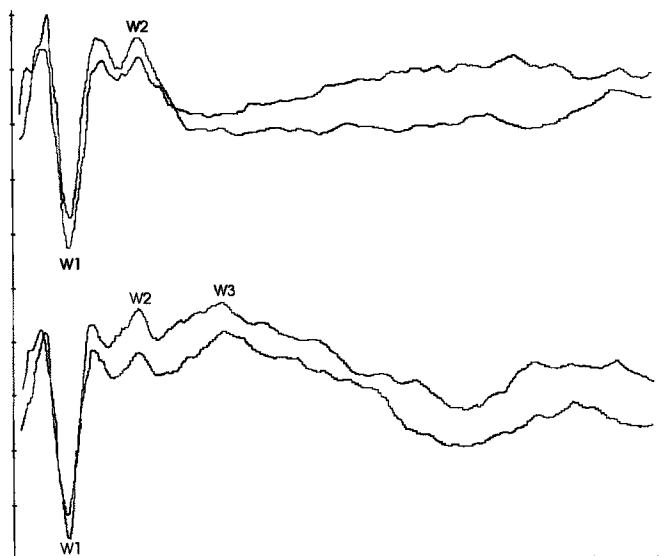


Figure 1. Scalp recordings after stimulation of the infraorbital nerve immediately before (upper trace) and after (lower trace) microvascular decompression in Patient 2. Before microvascular decompression component W3 (the entry zone) was missing, whereas W1 (Gasserian ganglion) and W2 (retro-Gasserian) peak latencies were normal. After microvascular decompression, component W3 could be recorded, although its peak had a latency that exceeded normal limits (upper limits of normality for W1-to-W3 interpeak interval, 2.15 msec¹⁰). Calibrations are 1 msec per division for the x-axis and 0.75 μ V for the y-axis.

Methods. Patients. Ten patients with trigeminal neuralgia for 2 to 23 years were investigated. They were selected to have substantial involvement of the second division and to have arterial vascular compression demonstrated by preoperative MR tomoangiography using tech-

niques described previously.¹⁶ All patients gave informed consent to the procedure, which complied with the Helsinki Declaration of 1975, as revised in 1983. The study was approved by the local ethical committee.

Stimulation. Trigeminal evoked potentials were performed by selective electrical stimulation of the infraorbital nerve by means of two needle electrodes inserted into the ipsilateral foramen as described elsewhere.¹⁰ Positioning of the stimulating electrodes was performed immediately after the patient had been anesthetized.

Far-field scalp responses. A surface recording electrode was placed at the vertex (Cz), referenced to the neck (Cv7, seventh cervical vertebra), and recordings were performed approximately every 10 minutes during the whole operation, and specifically before and after microvascular decompression. The signals were amplified 200,000 times. Bandpass of the amplifiers was set at 10 to 3,000 Hz, 3-dB points, and at least 500 responses were averaged. The recordings were repeated no less than twice to confirm reproducibility. Because even small differences in depth insertion of the stimulating needles may give rise to a latency shift of all the trigeminal evoked potential components, the latency interval between the Gasserian ganglion (component W1) and the entry zone (component W3) peaks was measured to compare it with the upper limit of normality (2.15 msec) already published¹⁰ (obtained in 48 normal subjects from a mean value of 1.64 msec added to three times its SD of 0.17 msec). Definition of recovery of the nerve function within a single subject was that a latency shift of more than 0.13 msec occurred in the W1-to-W3 interpeak interval. The number 0.13 msec represents the upper limit of intraindividual variation (two recordings) of the given interval in normal subjects. This number was obtained in a previous work¹⁰ on 48 normal subjects based on the mean (0.04 msec) added to three times the SD of 0.03 msec (see table II in reference 10, p. 419).

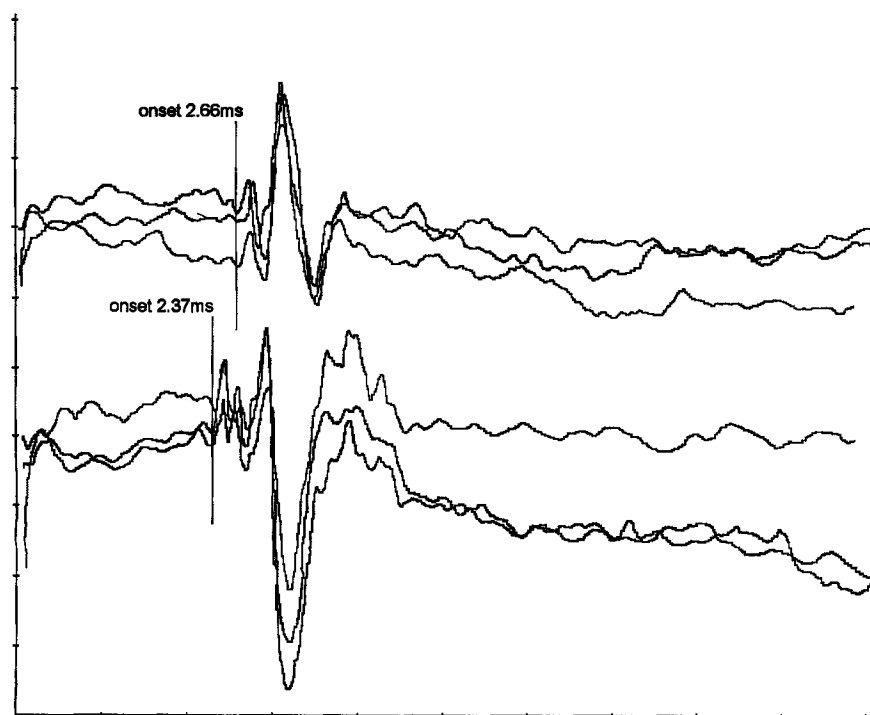


Figure 2. Direct recordings from the root after stimulation of the infraorbital nerve performed immediately before (upper trace) and after (lower trace) microvascular decompression in Patient 1. Onset of response (marked by a vertical line) is used here rather than peak latency because it offers better reliability in these recording conditions. Onset is at 2.66 msec before microvascular decompression, whereas it is anticipated to 2.37 msec after. Other changes take place after microvascular decompression: the principal component is larger in amplitude, and it is not only preceded, but also followed, by a number of wavelets representing groups of fibers conducting at different velocities. Calibrations are 1 msec per division for the x-axis and 10 μ V per division for the y-axis.

Table 1 Summary of patient scalp recordings

Patient no.	After induction of anesthesia (mean \pm SD)	n	Before MVD, root exposed (mean \pm SD)	n	Immediately post-MVD (mean \pm SD)	n	End of procedure (mean \pm SD)	n	Two days postoperatively (mean \pm SD)	n
1	2.43 \pm 0.02	3	2.44 \pm 0.02	3	2.14 \pm 0.01	3	2.15 \pm 0.01	3	2.13 \pm 0.02	3
2	W3 absent	2	W3 absent	2	2.36 \pm 0.007	2	2.34 \pm 0.007	2	2.34 \pm 0.007	2
3	2.70 \pm 0.03	3	2.70 \pm 0.03	3	2.50 \pm 0.03	3	2.50 \pm 0.02	3	2.35 \pm 0.03	3
4	W3 absent	2	W3 absent	2	2.78 \pm 0.007*	2	2.76 \pm 0.007	2	2.57 \pm 0.007	2
5	2.84 \pm 0.01	3	2.90 \pm 0.03	3	2.29 \pm 0.02	3	2.18 \pm 0.02	3	2.13 \pm 0.01	3
6	2.24 \pm 0.007	2	2.25 \pm 0.01	3	1.93 \pm 0.02	3	1.92 \pm 0.02	3	1.93 \pm 0.01	3
7	2.80 \pm 0.01	3	2.82 \pm 0.02	3	2.81 \pm 0.02	3	2.83 \pm 0.01	3	2.83 \pm 0.007	2
8	2.51 \pm 0.007	2	2.50 \pm 0	2	2.52 \pm 0.01	3	2.51 \pm 0.007	2	2.53 \pm 0.02	3
9	2.48 \pm 0	2	2.49 \pm 0.007	2	2.87 \pm 0.02	3	2.90 \pm 0.02	3	2.75 \pm 0.007	2
10	W3 absent	3	W3 absent	3	2.66 \pm 0.007	2	2.63 \pm 0.007	2	2.42 \pm 0.01	3

Intervals (expressed in msec) between peaks of W1 and W3 components of scalp trigeminal evoked potentials at various stages of operation and at follow-up. Each value is the mean obtained from two or three immediately successive recordings. SDs are reported, as well as the actual number of recordings (n). Differences ≥ 0.13 msec have been considered significant to a change.¹⁰ All intervals > 2.15 msec are considered abnormal.¹⁰

* In Patient 4, this recording was taken 30 minutes after root exposure. Two vessels had to be removed from the root, and recovery was demonstrated only after removal of the second vessel.

MVD = microvascular decompression; W1 = Gasserian ganglion; W3 = entry zone.

Direct root recordings. Responses were recorded directly from the root after it had been exposed and after decompression. Two 1-mm silver ball electrodes, with an intertip distance of 2 mm, were mounted in a holder in a forklike manner. Using the operating microscope they were placed transversely over the root, proximal (with reference to the pons) to compression. A second set of recordings was made following decompression from the site, which was identified visually and recorded on videotape. The surgeon repositioned the electrodes as closely as possible to the original site—measurements made in one subject showed that this was done to within ± 1 mm. Signals were fed into amplifiers with 5 to 5,000 Hz bandpass (3-dB points) with gain of 20,000 times. To check reproducibility, the whole procedure was repeated three times before and after decompression, and data were accepted only when the responses had the same onset latency (within ± 0.05 msec) and waveform. In contrast to the scalp responses, in which peak-to-peak latencies were considered, the absolute latencies of response onsets were deemed more reliable in the case of the root. This was so because the morphology of the root response could change between pre- and postmicrovascular decompression. This choice was also justified by the response from the root being a near field, just representing activation of the tract beneath the electrodes. To provide consistency with the scalp recordings, changes in latency were considered significant only when larger than 0.13 msec.

Amplitude changes in either scalp far-field or root recordings were considered significant only when changes were greater than 50%.

Results. On operation, all patients were found to have neurovascular compression caused by an artery. In one patient (Patient 4), dual-vessel compression was identified.

Far-field scalp recordings. Table 1 summarizes the results obtained in our patients from scalp recordings. All patients had an altered scalp response before operation, consisting of delayed or absent W3, suggesting conduction impairment at the root entry zone. Patients 1 through 6 and 10 showed recovery or normalization of the scalp response a few minutes after decompression (figure 1). In Patient 4, immediately after the surgeon removed a vessel deemed responsible for the neuralgia, no modification of the response was seen. However, removing this vessel made another vessel visible, which obviously distorted the root. On removal of the second vessel, the response recovered immediately, and was found to be completely normalized on follow-up. Patients 7 and 8 showed no modification after surgery. In Patient 9, during manipulation of the root, a slight reduction in amplitude and an increase in delay of W3 took place.

Direct root recordings. In table 2 the results from root recordings are shown. In the first six patients there was a reduction in latency of the onset of the response recorded (figure 2), which paralleled the reduction in latency of the peak of the W3 component from the scalp. Amplitudes of the root responses showed changes large enough to be considered (larger than 50%) only in Patients 2, 4, and 10, who demonstrated an increase after decompression. In these patients, scalp W3 could not be recorded before decompression but appeared after decompression.

All 10 patients were pain free postoperatively. No sensory deficits were detected, even in the patient with worsening of the trigeminal evoked potential.

Discussion. Both scalp far-field and root recordings were in agreement in detecting recovery of the

Table 2 Direct root recordings

Patient no.	Before MVD, root exposed (mean \pm SD)	n	Immediately post-MVD (mean \pm SD)	n	Difference n
1	2.66 \pm 0.01	3	2.37 \pm 0.02	3	0.29, $p < 0.0001$
2	3.22 \pm 0.02	3	2.54 \pm 0.02	3	0.68, $p < 0.0001$
3	2.94 \pm 0.02	3	2.69 \pm 0.01	3	0.25, $p < 0.0001$
4	3.18 \pm 0.02	3	2.71 \pm 0.01	3	0.47, $p < 0.0001$
5	2.92 \pm 0.02	3	2.37 \pm 0.03	3	0.55, $p < 0.0001$
6	2.57 \pm 0.02	3	2.23 \pm 0.02	3	0.34, $p < 0.0001$
7	3.16 \pm 0.03	3	3.16 \pm 0.02	3	0.00, NS
8	2.67 \pm 0.02	3	2.69 \pm 0.03	3	-0.02, NS
9	2.7 \pm 0.03	3	3.12 \pm 0.02	3	-0.39, $p < 0.0001$
10	3.26 \pm 0.04	3	2.75 \pm 0.03	3	0.51, $p < 0.0001$

Onset latencies (expressed in msec) of response recorded from the root before and after microvascular decompression. Each value is the mean obtained from two or three immediately successive recordings. SDs are reported as well as the actual number of recordings (n). All differences are highly significant (*t*-test, unpaired, two tailed; $p < 0.0001$) with the exception of Patients 7 and 8 (no significant difference), who were considered unchanged.

MVD = microvascular decompression; NS = not significant.

nerve function in seven of 10 patients immediately after microvascular decompression. Recording far fields from the scalp proved extremely stable, with electrodes left in place throughout the operation, demonstrating that peak latencies were not affected by environmental conditions. The scalp recordings performed in our patients before decompression showed that in all patients a subclinical impairment in conduction along the high-medium velocity fibers occurred in the region of the root entry zone. This finding is consistent with the site of compression seen by MR tomoangiography and in accordance with electrophysiologic studies of idiopathic trigeminal neuralgia and other lesions (tumors) at the root entry zone reported previously in the literature.¹³ We presume that the universal occurrence of impairment in our patients, in contrast to the lower frequency of abnormalities in previous reports,¹³ is a result of the selection of patients for this study based on the knowledge that arterial neurovascular compression was present, as shown by MR tomoangiography and confirmed on operation.

Root recordings were of the near-field type; therefore, only the activity of fibers underlying the electrode tip would be detected. In contrast to scalp recordings, they could be affected by the electrode position, and the amplitude of the response might be influenced by the degree of pressure exerted against the root. Because the electrode was removed from the nerve for decompression, this greatly increased the variability intrinsic to this type of recording. Nevertheless, with the precautions described in the Methods section, it was possible to ensure that reliable and stable recordings were performed before and after decompression. These recordings showed a substantial improvement in the same seven patients in

whom the scalp evoked responses had recovered, thus providing a strongly concordant result.

The recovery of delayed or absent scalp W3 and of the root recordings in the same patients clearly showed that nerve conduction was improved during the operation, and we believe this to be the first neurophysiologic evidence available so far of the immediate effect of the surgical procedure. Because all the electrophysiologically improved patients also experienced pain relief, one might conclude that recovery of trigeminal evoked potentials is a predictor of pain relief, which has important implications regarding the mechanisms of production of trigeminal pain. However, even those patients in whom the trigeminal evoked potentials showed no recovery (Patients 7 and 8) or worsened (Patient 9) were pain free. Two explanations may be that 1) the mechanism of pain relief is identical in these patients as in all other patients and it is the perioperative trauma that has prevented normalization or has caused worsening of the evoked response, or 2) in these patients the trauma to the nerve is responsible for the immediate pain relief, and the microvascular decompression was perhaps responsible for its long-term maintenance. Partial rhizotomy is a successful treatment for trigeminal neuralgia; so, clearly, it is possible for trauma to provide pain relief. The disturbance of the nerve produced by the neurovascular conflict might produce pain by separate actions from that by which the neurophysiologic disturbance is created. Thus these events would be closely correlated but not directly related.

In Patient 9 deterioration in the evoked potentials indicates that manipulation of the root had caused damage to it (albeit subclinical), and although it is possible that in this patient the neuralgic pain was

relieved through mechanisms similar to a thermorhizotomy (i.e., by damaging some fibers), this may be unlikely because there was no new detectable sensory deficit present in this patient postoperatively. Patient 9 indicates that subclinical trauma (postoperatively sensation was normal) can be detected using these methods, implying its absence in the patients showing immediate improvement. In the patients showing immediate improvement in latency and amplitude, and in whom sensation is normal postoperatively, it is then difficult to imagine that trauma plays a significant role in the mechanism of action of the operation.

It is also necessary to explain the rapidity of the recovery, which is immediate. Fast recovery from conduction impairment is only possible in nerves that have suffered mild compression. Such condition is described as "rapid reversible physiologic block"¹⁷ or "class 1 of nerve injuries."¹⁸ From a symptomatic point of view, it is well known that decompression of the median nerve in carpal tunnel syndrome relieves pain and paresthesias immediately in the innervated area, and such quick recovery has also been documented electrophysiologically in carpal tunnel syndrome¹⁹ and in animals.^{20,21} Furthermore, abnormal trigeminal evoked potentials in a patient with a tumor of the cerebellar-pontine angle showed recovery a few days after successful removal of the tumor, together with normalization of the previous sensory deficit (Patient 8 in reference 13). This argues against demyelination as a requirement for pain,^{22,23} because remyelination could not occur within this time scale. We hypothesize that our patients had a class 1 nerve injury to the trigeminal root, causing rapidly reversible ischemic and metabolic changes in the nerve that resulted in both the production of pain and conduction impairment in fast-conducting axons of the root (the slower conducting fibers could not be examined because of the much smaller amplitude and time dispersion of their responses). Relieving the compression would restore normal conditions, thus interrupting the pain-producing mechanism and greatly relieving the conduction impairment. One may speculate that the late, slight improvement of nerve conduction is a result of a slower remyelination process that, however, would be of no relevance to pain relief, which occurred much earlier. In addition to the theoretical considerations consequent on the rapid restoration of electrophysiologic data, it is worth considering the practical value of the phenomenon, which is best illustrated by Patient 4, in whom improvement did not occur until the second vessel was decompressed. In 16% of patients multiple vessels are present,¹⁶ so this is a significant clinical problem. Although sensitivity and specificity cannot be ascertained from such a small number of patients, the technique may provide a means of supplying surgeons immediate information regarding the effects of their maneuvers and some insight regarding which is the significant vessel.

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The wide spectrum of myofibrillar myopathy suggests a multifactorial etiology and pathogenesis

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Article abstract—*Background:* Myofibrillar myopathy (MFM) is characterized by nonhyaline lesions (foci of myofibrillar destruction) and hyaline lesions (cytoplasmic inclusions composed of compacted myofibrillar residues) on light and electron microscopy. Immunocytochemistry demonstrates the abnormal expression of desmin and numerous other proteins. The clinical, laboratory, and histologic features of MFM are heterogeneous, making a diagnosis difficult. *Results:* We diagnosed eight patients with MFM over the preceding 3 years. MFM was inherited in an autosomal dominant pattern in one patient, developed sporadically in five patients, and was induced by an experimental chemotherapy, Elnafide (Knoll, Parsippany, NJ), in two patients. Age at onset ranged from 14 to 64 years. The pattern of weakness was variable but involved proximal and distal muscles. Five patients had evidence of a cardiomyopathy. Electromyography demonstrated muscle membrane instability and small, polyphasic motor unit potentials. Serum creatine kinase levels were normal to moderately elevated ($<10\times$ normal). Light and electron microscopy demonstrated the characteristic pattern of nonhyaline and hyaline lesions and the associated abnormalities on immunocytochemistry. *Conclusions:* Patients demonstrate a wide spectrum of clinical, laboratory, and histologic abnormalities. Chemotherapy-induced MFM has abnormalities on immunocytochemistry similar to the those of hereditary and sporadic cases. The pathogenesis of MFM is likely heterogeneous. However, MFM is distinctive in that it can preferentially affect distal muscles and has a frequent association with cardiomyopathy. The cardiomyopathy may be amenable to treatment with pacemaker insertion or cardiac transplantation.

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Myofibrillar myopathy (MFM) is a rare, often overlooked disorder characterized by two major histopathologic abnormalities: nonhyaline lesions consisting of foci of myofibrillar destruction and hyaline lesions composed of compacted and degraded myofibrillar elements.¹⁻³ Abnormal expression of desmin has been shown in muscle fibers on immunostains.¹⁻⁵ However, desmin is not the only protein that is abnormally expressed with immunostaining. Studies from the Mayo Clinic demonstrated that the nonhyaline lesions react strongly to desmin, dystrophin, gelsolin, neural cell adhesion molecule (NCAM), and the N-terminus of β -amyloid precursor protein (β -APP).² They are depleted of actin, α -actinin, and myosin and less consistently, of titin and nebulin.² The hyaline lesions react to dystrophin, gelsolin, the N-terminus of β -APP, titin, nebu-

lin, actin, α -actinin, and myosin but not to NCAM and are variably reactive to desmin.² Both types of lesions are congophilic. Furthermore, the abnormal muscle fibers demonstrate abnormal expression of cell division cycle 2 (CDC2) kinase and other cyclin-dependent kinases (CDKs)—CDK2, CDK4, and CDK7.³ Thus, the term “myofibrillar myopathy” has been recommended as a more accurate description of the spectrum of the histologic abnormalities.¹⁻³

Confusion may arise because MFM has been reported previously as desmin storage myopathy,⁵ desmin myopathy,⁶ familial desminopathy,⁷ spheroid body myopathy,^{8,9} cytoplasmic body myopathy,¹⁰⁻¹⁶ Mallory body myopathy,¹⁷ familial cardiomyopathy with subsarcolemmal vermiform deposits,¹⁸ and myopathy with intrasarcoplasmic accumulation of dense granulofilamentous material.¹⁹ In addition,

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● *Original Contribution***LOW-INTENSITY PULSED ULTRASOUND ACCELERATES THE
REGENERATION OF THE SCIATIC NERVE AFTER NEUROTOMY IN
RATS**

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Abstract—The biophysical qualities of pulsed ultrasound (US) led us to appraise its effect on the regeneration of a peripheral nerve. In this study, our intention was to evaluate the effects of pulsed US on the axotomy of the sciatic nerve in rats. The proximal stump of the nerve was stimulated on 12 consecutive days with pulsed US and the effects of the sonication were evaluated through morphological and morphometric techniques. Our findings suggest that sonication leads to a rapid regeneration of the nerve after axotomy. These affirmations are based on the counting of different types of fibre components in mixed nerves and the morphological recovery of the same in comparison with nerves of animals submitted to sham operation. (E-mail: criscicozac@netsite.com.br) © 2002 World Federation for Ultrasound in Medicine & Biology.

Key Words: Low-intensity pulsed ultrasound, Peripheral nerve, Regeneration.

INTRODUCTION

The regeneration of peripheral nerves is already an established fact and, for this reason, a continuous search has been made for factors, mechanisms or techniques that can help to restore them.

Investigations with the same objectives were undertaken using autologous grafting (Foidart et al. 1997), endoneurium components of peripheral nerves (Labrador et al. 1998) or, as in Evans et al. (1999), by the use of grafting preserved by refrigeration and thawed before use.

However, few works have aimed at using physical stimulus or any other noninvasive methods in the regeneration of peripheral nerves. This fact led us to test the effects of low-intensity pulsed ultrasound (US) in a prospective way, with the purpose of studying its eventual action on the regeneration of a mixed peripheral nerve. The sciatic nerve of a mouse was selected, so that the action of low-intensity US could be evaluated on the regeneration of this mixed nerve, after its experimental neurotomy.

The low-intensity pulsed US was initially thought of and used in the repairing of pseudarthrosis and bone

fractures by Duarte (1983), when it was found to be active in the formation of new bone tissue and in the repairing of fractures. Its relation to, and its effects on, osteogenesis are reported in a recent survey by Rubin et al. (2001).

Other biologic tissues also responded satisfactorily to the stimulus of low-intensity pulsed US: Nolasco (1993), in skin healing of alloxanic diabetic rats; Hilario (1993), in the repair of chronic varicose ulcers; Pires (1994), in the resolution of chronic inflammatory process; and others. A neurotomy is an adequate model for the study of cellular response to injury (Koliatsos and Price 1996) because repair is made by a typical healing process. Because this model is easily reproduced and characterised as a typical initial acute inflammatory reaction, it was decided to use this noninvasive method in the regeneration of an experimental neurotomy of the sciatic nerve in rats. According to Dyson and Paookes (1983), low-intensity US, when used in the first 15 days of the inflammatory phase, manifests more intensely its healing effects.

MATERIALS AND METHODS

To carry out the present investigation, 35 Wistar rats of both genders, whose weights varied from 120 g to 150 g, were used.

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For the morphological evaluations, 25 animals were reserved and, for the morphometric evaluations, 10 animals. After anesthesia and asepsis, surgical access for exposing the sciatic nerve was carried out through perpendicular section of all the fibres of the maximus gluteus muscle, which, after being separated, permitted the visualisation of the sciatic nerve. Following this, neurotomy with ophthalmic scissors was carried out. In the group made up of 25 rats, 13 received applications of low-intensity pulsed US and 12 received a sham sonication that served as a control for the stimulated ones. For the morphometric evaluation, 10 more animals whose sciatic nerves were neurotomed on both sides were used. Only the nerve of the right side was stimulated, and the other side served as a control and received only a sham stimulation.

The Ethics Council of our University certified that this research project was within the ethical norms for animal experiments.

Application of low-intensity pulsed ultrasound

At 24 h after neurotomy, daily applications of low-intensity pulsed US were initiated on the site where the axotomised nerves had been, obeying the following rules:

1. Daily, 20-min applications, always at the same time of day, during 12 consecutive days.
2. The applications were motionless and a thick layer of hydro gel was used before the coupling of the transducer.

The control group was not stimulated, but underwent identical treatment without the pulsed US stimulus.

Preparation for morphological studies

After the stipulated sonication period, we conducted the removal of proximal nerve stumps of nerves for histotechnical procedures to be carried out. With the aim of getting a fast and early fixation of the proximal nerve stumps, after the anesthesia of animals and their exposure, glutaraldehyde was dripped to achieve fixation. After euthanising the animals by excessive inhalation of ether, the proximal stumps were then identified and submitted to routine steps for inclusion in araldite and for the acquisition of fairly fine sections. The sections, after being stained with toluidine blue, were examined under a light microscope and photographed at various close-up ranges.

From the fairly fine blocks, ultrafine sections for structural evaluation were made.

Equipment generator of ultrasound and parameters used in the experiment

The equipment used consisted of a US stimulator, designed and built in the Engineering Laboratory of the

São Carlos Engineering School, São Paulo University, and the standards used for the ultrasonic stimulation were as follows: power 96.04 mW; type of wave: pulsed; acoustic intensity 16 mw/cm (SATA); length of pulse 200 ms; repetition frequency 1 kHz; amplitude 25 V (peak to peak); frequency of PZT-4, 1.5 MHz.

Morphometric and morphological analyses

The statistical evaluations were made by comparing the neurotomed nerves, treated or untreated, with the paired *t*-test.

From the sections of the proximal stumps of stimulated or nonstimulated nerves, photographs of five random fields, totaling 100 photographic fields, were made and stored in disk drives for zipping. In this way, almost the whole area of the nerve contained in the transverse semifine section was photographically traced for the morphometric study of its different structural components.

With the software application (UTHSCSA Image Tool)¹, the following parameters were studied:

1. Number of different kinds of component fibres of the mixed nerve.
2. In type A fibres (fast conduction), both the thickness of the myelin sheath and the axons area were estimated.

Image Tool software also provides the simultaneous capacity of estimating the number of fibres, the thickness of the myelin sheath and the axon areas as well. The data obtained were stored in another program (Excel) and later statistically analysed by means of the program Sigma Stat 2.03.

RESULTS

Morphological analysis

It was agreed to analyse the proximal stump of the axotomised nerves, starting from the sectioned area in the centripetal direction, along the cellular body.

Figure 1 shows the morphological findings of the sectioned area of the stimulated proximal stumps in which a smaller number of cells can be found, arranged as an amputation neuron and, in subsequent cuts, irregular and deformed myelin sheaths. In the photomicrographs Fig. 1, from stimulated animals, we notice the existence of newly formed vessels in the sectioned area, as well as a larger quantity of nonorganised cells in the amputation granuloma and, in the subsequent section, thicker myelin sheaths arranged with regularity and showing few deformations.

¹ Developed at the University of Texas Health Science Center at San Antonio, TX, and available from the Internet by anonymous FTP from maxrad6.uthscsa.edu.

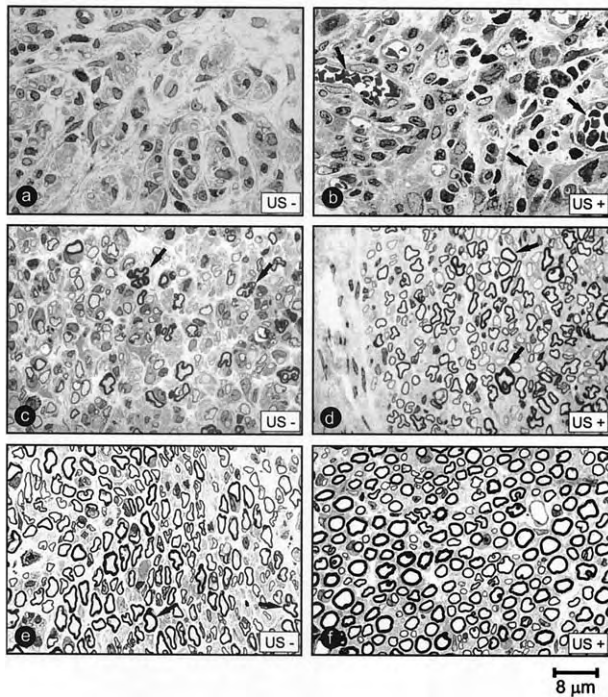


Fig. 1. Photomicrograph of semifine sections stained with toluidine blue in a sciatic nerve stump transverse section. (a) The nonstimulated severed nerve area of a proximal stump; the cells organised like an amputation neuroma. (b) The distal extremity of the proximal stump, with a higher number of newly formed vessels (arrow) and of precursory Schwann cells (arrow). Proximal stump fibres of (c) the unstimulated nerve and (d) stimulated nerve with the quality and characteristics of the same unraveled myelin sheath. (e) Proximal stump fibres of the nonstimulated nerve: the myelin sheaths present irregularities, and many show crenation (arrow). (f) Proximal stump fibres of the stimulated nerve, showing the regularity of the myelin construction.

Figure 2, obtained from areas closer to the nerve stumps, shows transverse as well as longitudinal sections, the regularity of the form and the constitution of the myelin sheaths, in stimulated stumps and, in the nonstimulated stumps, different types of deformity in the myelin sheaths were revealed.

Figure 3 focuses on the perineurium of a nonstimulated nerve (Fig. 2a) and the perineurium of stimulated nerves (Fig. 3). These appear to be thicker and more organised.

Table 1. Number of myelin fibres A-type

Treatment	Mean	SD	Standard error
Control (USP-)	18.160	3.487	1.103
Ultrasound (USP+)	46.190	2.245	3.872

$p < 0.001$.

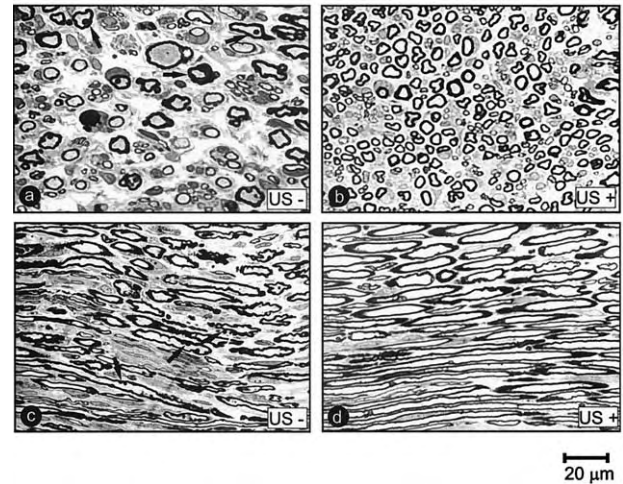


Fig. 2. Photomicrograph of semifine sections of the sciatic nerve, stained with toluidine blue. (a) Proximal stump fibres of unstimulated nerve in transverse section, with bizarre aspects of the myelin sheath disposition and altered composition of the constituent fibres of sciatic nerve, axonal atrophy (arrow) and uncoiled myelin sheath (arrow). (b) Proximal stump fibres of the stimulated nerve, showing regularity of sheaths and the amount of component stump fibres, in transverse section. (c) Proximal stump fibres of unstimulated nerve in longitudinal section, showing the bizarre aspects of the myelin sheath. (d) Proximal stump fibres stimulated in longitudinal section.

The sequence of Figs. 4 to 6 are electromicrographs for the morphological comparative evaluation between the different constituents of the nonstimulated and stimulated nerves.

Figure 4 presents, in electromicrographs, the myelin sheath of nonstimulated nerves showing different kinds of deformities, possibly because of regeneration deficiency, also exhibiting Schwann cells with morphological characteristics that may be attributed to low metabolic activity.

Electromicrograph Fig. 4 shows defects of axoplasm and of its organelles such as deformity (gap) and edematous mitochondria.

Figure 4 electromicrographs of stimulated nerves show well-constituted myelin, Schwann cells with characteristics of increased metabolic activity and axoplasm with its different components well preserved.

Figure 5 exhibits details of nonstimulated nerve

Table 2. Number of myelin fibres B-type

Treatment	Mean	SD	SE
Control (USP-)	39.080	3.506	1.109
Ultrasound (USP+)	66.960	11.158	3.528

$p = 0.004$.

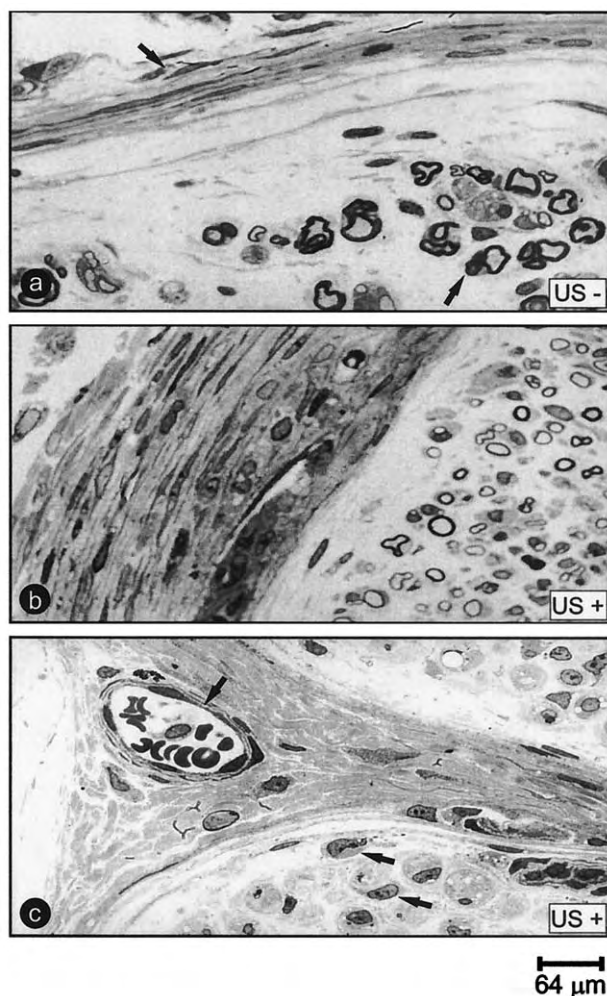


Fig. 3. Photomicrograph of semifine section of the sciatic nerve stained with toluidine blue. (a) Proximal stump fibres in transverse section of a nonstimulated animal, showing bizarre aspects of the myelin sheath disposition and of the altered composition of constituent fibres of sciatic nerve, axonal atrophy (arrow) and atrophy of the connective tissue the middle layer, perineurium (arrow). (b) and (c) Proximal stump fibres of the stimulated nerve, showing regularity of the sheaths and number of component fibres of the stump, in transverse section, and the composition of connective tissue investments of the perineurium, showing increase of collagen fibres, with blood vessel (arrow).

fibres and of stimulated fibres. In the former, as demonstrated in the perineurium semifine sections, there is

Table 3. Number of amyelinic fibres

Treatment	Mean	SD	SE
Control (USP-)	1.840	0.556	0.176
Ultrasound (USP+)	1.710	0.706	0.223

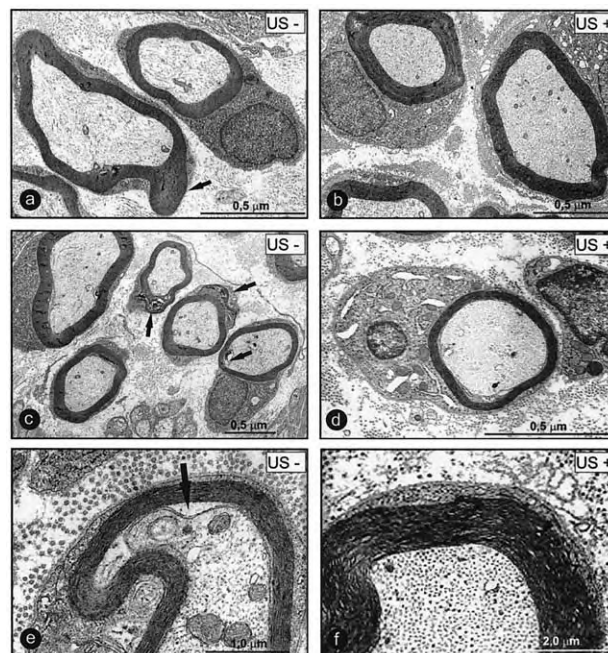


Fig. 4. Electromicrograph of the sciatic nerve. (a) Abnormal myelin sheaths observed in nonstimulated nerve stumps, showing myelin sheath crenation (arrow). (b) Normal myelin sheaths in nerve stumps that received the stimulus. (c) Myelin sheath with abnormal characteristics of stumps that did not receive sonication with the pulsed US, showing the presence of partial clefts (arrow). (d) Myelin sheath and Schwann cell with normal aspects of stumps that received stimulus with pulsed US. (e) Myelin sheath of nerve stump that did not receive stimulus, partial slit detail (arrow). (f) Myelin sheath detail and axoplasm of stumps that received sonication with pulsed US.

deficiency in the quantity of collagen fibrilles, in comparison to the electromicrographs of stimulated nerve. The axoplasm parts in nonstimulated fibre were disarranged but, in the stimulated fibre, they exhibit normal disposition and constitution.

Figure 6 shows electromicrographs of stimulated Schwann cells and nonstimulated cells. In Fig. 6, Schwann cells exhibit morphological characteristics in accordance with the increased metabolic activity (Junqueira and Carneiro 2000), while electromicrographs of nonstimulated cells, the morphological characteristics indicate low functional activity. The characteristics of

Table 4. Myelin sheath thickness (μm)

Treatment	Mean	SD	SE
Control (USP-)	0.108	0.0526	0.0186
Ultrasound (USP+)	0.173	0.0462	0.0163

$p = 0.023$.

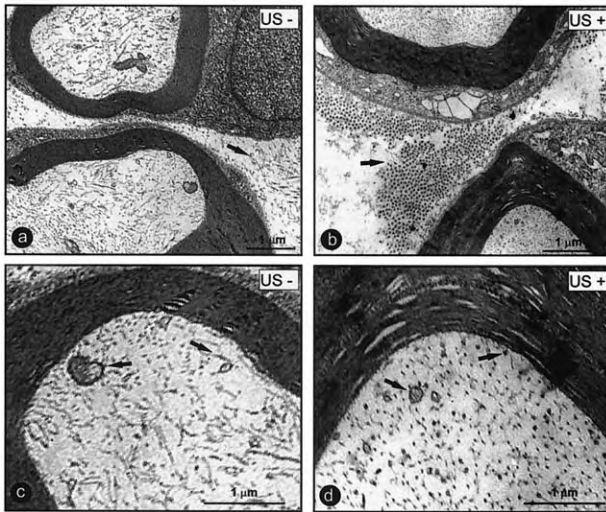


Fig. 5. Sciatic nerve electromicrograph of animals. (a) Endoneurium, with a reduction of collagen fibrilles in nonstimulated stumps. (b) Endoneurium, with increase of collagen fibrilles in stimulated stumps. (c) Axoplasm, with edematous mitochondrion (arrow), agranular vesicles (arrow) and disperse microfilamentum (arrow) in nonstimulated stump. Axoplasm with stimulated stumps, in which a higher quantity of neurotubules (arrow) and small agranular vesicles (arrow) can be observed.

chromatin and of nuclear membrane are those of low metabolic activity cells.

Quantitative evaluations

The numbers of A-type fibres presented statistically significant differences ($p < 0.001$), representing a more intense temporal regeneration in the stimulated animal nerves. Table 1 and the diagram (Fig. 7) are representative of our findings.

B-type fibres also presented statistically significant differences ($p = 0.004$) between nerve stumps of stimulated and nonstimulated animals. Table 2 and the diagram (Fig. 8) are representative of numerical frequencies of B-type fibres.

On the other hand, C-type fibres (amyelinic) have not presented statistically significant differences, as represented in Table 3 and diagram (Fig. 9).

Figure 10 shows a histogram of the group of average values corresponding to the quantity of different

Table 5. Axon area (μm)

Treatment	Mean	SD	SE
Control (USP-)	0.136	0.0477	0.0169
Ultrasound (USP+)	0.212	0.0676	0.0239

$p = 0.049$.

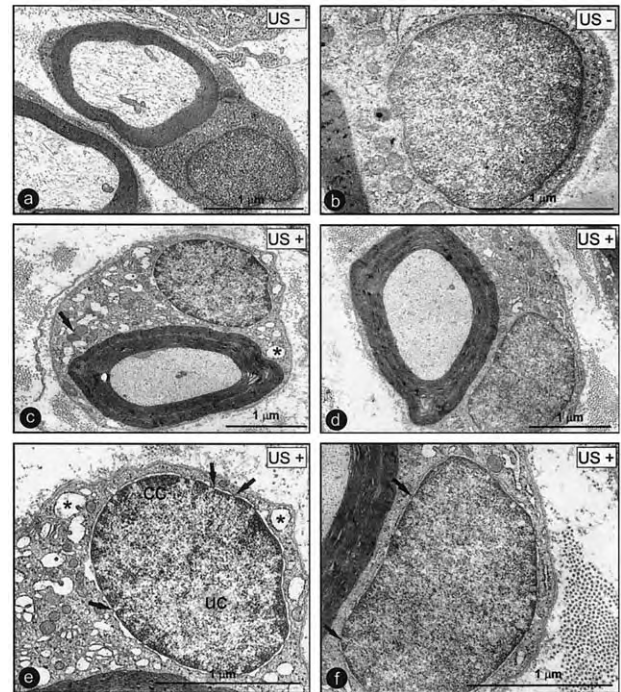


Fig. 6. Electromicrograph of sciatic nerve of animals. (a) Schwann cell surrounding myelinated fibre in stump of the nonstimulated group. (b) Schwann cell nucleus of nonstimulated animal. (c) Schwann cell of stimulated stump with active cytoplasm; note the high number of mitochondria (arrow) and endoplasmic reticulum (asterisk). (d) Schwann cell in stimulated nerve. (e) The Schwann cell nucleus shows areas of more condensed chromatin (cc) near nuclear membrane and large areas of uncoiled chromatin (uc). The nuclear membrane pores (arrows) are present in large quantities in the stimulated nerve. (f) Schwann cell nucleus in detail; the nuclear membrane pores (arrows) are more numerous in stimulated cells.

types of fibres estimated in the control and stimulated nerves.

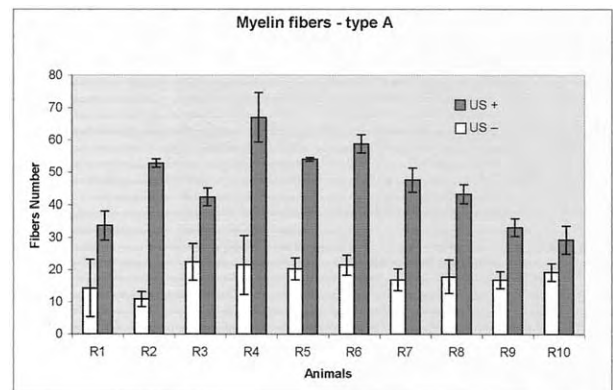


Fig. 7. Diagrammatic representation of the counting of type A myelin sheaths.

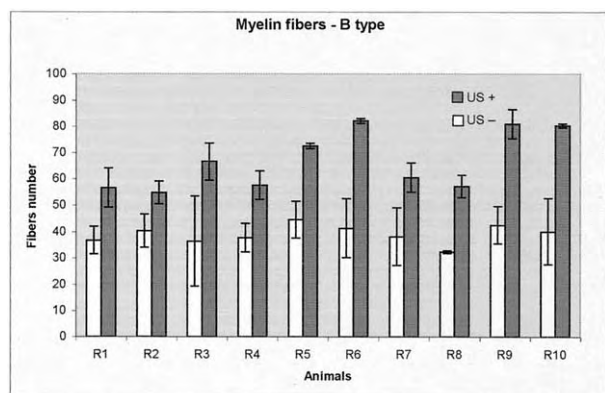


Fig. 8. Diagrammatic representation of the counting of type B myelin fibres.

In Figs. 11 and 12, the thickness values of the myelin sheaths of A-type fibres and the axon area of stimulated and nonstimulated fibres are shown. Both the sheath thickness and A-type fibre axon area in the stimulated nerves show statistically significant differences ($p = 0.023$) and ($p = 0.049$), respectively.

In Tables 4 and 5 the average values and SDs of those parameters are given.

DISCUSSION

Moore et al. (2000), using the effects of pulsed US in latency evaluation of human ulnar nerves, with 1-MHz and 870-kHz frequencies, and also in the evaluation of the sensory latency of the median nerve with 1- to 3-MHz frequencies, concluded that the alterations found in the nerve latency period occurred as a result of thermal effects, because high frequencies provoke rises in temperature. The use of pulsed US by these authors cannot be compared with low-intensity pulsed US because this

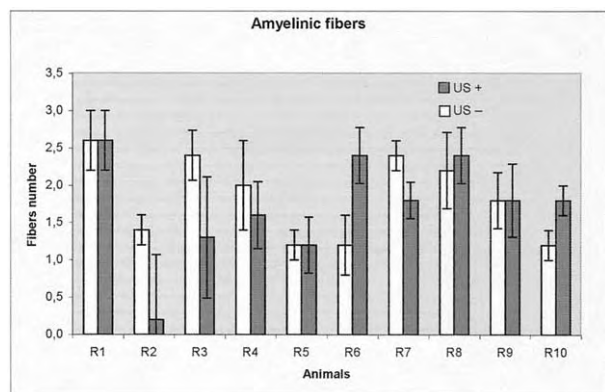


Fig. 9. Diagrammatic representation of the counting of amyelinic fibres.

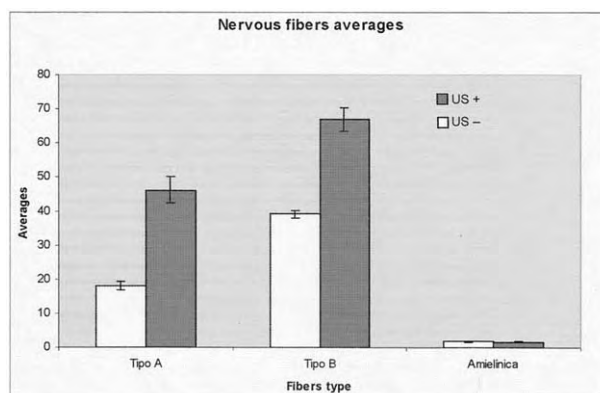


Fig. 10. Diagrammatic representation of the nervous fibre averages.

does not promote significant rise in tissue temperature, whereas, in other types of pulsed US, the beneficial or nonbeneficial effects apparently result from temperature rises. With the parameters of the ultrasonic beam optimised for therapeutic use, the rise in temperature at the site of application is about 1°C, suggesting, therefore, the participation of nonthermal mechanisms in the biologic action of low-intensity pulsed US (Dyson and Suckling 1978).

As far as the regeneration mechanisms are concerned, Rath et al. (1995) demonstrated that Schwann cells play a predominant role in peripheral nerve regeneration.

Madison et al. (2000) demonstrated that Schwann cells represent the richest source of netrin-1 protein in the peripheral nerve, which could play an important part in adult peripheral nerve regeneration. The electromicrograph morphological study of our investigation shows stimulus of Schwann cells through low-intensity pulsed US.

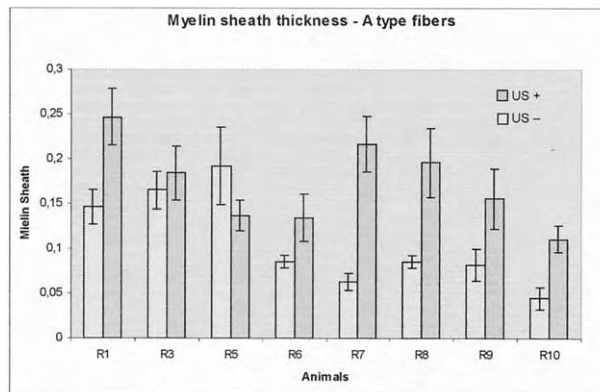


Fig. 11. Diagrammatic representation of the thickness of type A myelin sheath fibres.

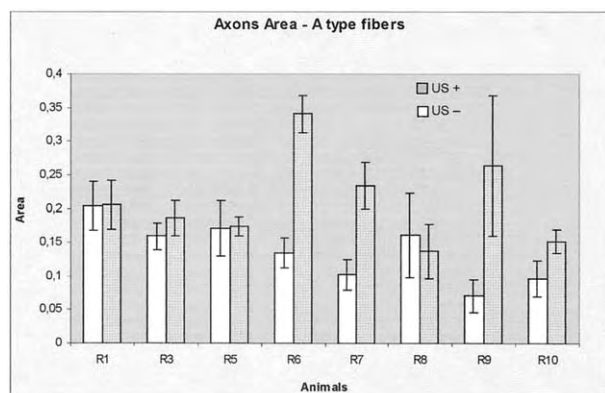


Fig. 12. Representation of the axon area of type A fibres.

Thus, the interest in finding supporting elements of peripheral nerve regeneration (Chien et al. 2000) would validate the use of low-intensity pulsed US as an attempt to add, with this method, a new factor to peripheral nerve regeneration, which was the main purpose of our research.

Our studies strongly suggest that the use of low-intensity pulsed US prompts a faster recuperation of the nerve after its neurotomy.

The larger number of thick (type A) fibres in the nerves of animals that received the stimulus undoubtedly arises from a stronger activity of the Schwann cells, when stimulated, leading to an earlier recovery of their myelin sheaths.

In relation to fine myelin fibres, the quantitative evaluations similarly suggest a faster recovery in the stimulated animals.

According to Araújo (1996), amyelinic fibres degenerate earlier and with greater intensity, which could explain a temporal delay in their numerical recovery; this can be deduced from the image in the diagram (Fig. 9), because the animals were sacrificed only after 24 h had elapsed from the last stimulus. Because low-intensity pulsed US is a noninvasive method, it could be associated with other factors already shown to be promoters of

peripheral nerve regeneration. This association would possibly lead to more favorable results.

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● *Original Contribution*

THE EFFECTS OF LOW-INTENSITY ULTRASOUND ON PERIPHERAL NERVE REGENERATION IN POLY(DL-LACTIC ACID-CO-GLYCOLIC ACID) CONDUITS SEEDED WITH SCHWANN CELLS

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Abstract—This study attempted to improve the efficacy of peripheral nerve regeneration, using the stimulus of low-intensity ultrasound (US) on poly(DL-lactic acid-co-glycolic acid) (PLGA) nerve guidance conduits seeded with Schwann cells. The possible differences between the ultrasonic effects of biodegradable and nonbiodegradable materials used as conduits were also investigated, by comparison with a group of silicone conduits. The PLGA conduits were seeded with or without Schwann cells (6×10^3 cells). All conduits were implanted 10 mm into right sciatic nerve defects in rats and underwent 12 ultrasonic treatment sessions over 2 weeks. Ultrasound was applied at a frequency of 1 MHz and an intensity of 0.2 W/cm² spatial average temporal peak (SATP) for 5 min/day. Histologic analysis was used to evaluate the recovery of the nerve after 6 weeks. Ultrasonically stimulated animals, especially those whose PLGA conduits, seeded with Schwann cells, exhibited considerably more myelinated axons with a larger mean area at the midconduit of the implanted grafts than those in any other group. Ultrasonic stimulation of a silicone conduit induced the generation of mass fibrous tissues that covered the nerve conduits and retarded axon regeneration. These results showed that ultrasonic stimulation may directly stimulate the seeded Schwann cells within the PLGA conduits to regenerate nerves. Nevertheless, the applying of US may not allow incorporation with the silicone rubber as a material from which to form nerve guidance conduits. © 2004 World Federation for Ultrasound in Medicine & Biology.

Key Words: Ultrasonic stimulation, Schwann cells, Nerve regeneration, Poly(DL-lactic acid-co-glycolic acid), Silicone conduit.

INTRODUCTION

Autologous nerve grafts have commonly been used in bridging peripheral nerve defects (Terzis et al. 1997). However, the limited availability and donor-site morbidity of autografts are the primary limitations on clinical applications. Enormous effort has been made to generate alternative, synthetic nerve conduits (Aldini et al. 1996; Archibald et al. 1991; Tountas et al. 1993). These synthetic conduits can help axonal proliferation, including a scaffold, support cells (i.e., Schwann cells and macrophages), induction factors and extracellular matrices (Gregory et al. 2000).

Adding lumen-occupying substances, such as extracellular matrix (ECM), nerve growth factor (NGF) and other neurotrophic agents, has been shown to promote the growth of axons (Fine et al. 2002; Yoshii et al. 2002; Verdu et al. 2002). Directly introducing cultured Schwann cells into

nerve conduits as persistent sources of neurotrophic factors is another effective mean of bridging a wide-ranging defect. Investigators have also demonstrated that cultured Schwann cells will persistently elaborate neurotrophic factors (Tessa et al. 2000; Gregory et al. 2002), construct neuronal cytoarchitecture (Li and Raisman 1997) and successfully regenerate myelin axons (Levi and Bunge 1994; Levi et al. 1994).

According to the literature, local events in the environment of an injured peripheral nerve trunk may importantly affect the functional capacity of seeded cells (Douglas 2000). The damaged regions of the surgery trauma are complex and replete with local thrombosis, ischemia and nitric oxide and are not appropriate for the culturing of seeded cells. Most seeded cells (80 to 90%) die during the grafting procedure or thereafter (Zawada et al. 1998; Barker et al. 1996; Mahalik et al. 1994). Accordingly, the restitution of injured surgery environment is substantial for a repaired nerve.

Low-intensity pulsed ultrasound (US) has a therapeutic effects on soft tissues, including inducing the recovery of a conduction block of the median nerve (Paik et al. 2002), the

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acceleration of wound healing (Dyson 1990), the acceleration of tendon healing (Enwemeka et al. 1990), an improvement on blood flow in a chronically ischemic muscle (Hogan et al. 1982), angiogenesis in the incision of the skin (Young and Dyson 1990) and acceleration of the healing of ischemic varicose ulcers (Dyson 1976). Crisci and Ferreira (2002) established that low-intensity pulsed US promoted the regeneration of the sciatic nerve after neurotomy in rats and an electromicrographic morphologic study revealed that Schwann cells were stimulated. However, no study has employed an ultrasonic stimulus to restore the functions of seeded Schwann cells in a synthetic guiding channel to improve peripheral nerve regeneration.

This investigation applied low-intensity US to Schwann cell-seeded poly(DL-lactic acid-co-glycolic acid) (PLGA) conduits to bridging a 10-mm defect of sciatic nerves in rats. Silicone conduit and autograft were also conducted in control groups. Histologic analysis was performed to assess the regeneration of the nerve.

MATERIALS AND METHODS

Culture of Schwann cells

Schwann cells were obtained according to the method of Grothe et al. (2000). Sciatic nerves of 3-day-old Sprague–Dawley rats were harvested and incubated in Liebovitz's L15 (Gibco, Invitrogen Co., Carlsbad, CA, USA), and washed 3 times with phosphate-buffered saline (PBS, pH 7.4). The epineurium was separated and nerves were dissected into discrete fascicles (less than 1 mm), which were enzymatically dissociated using 0.03% type I collagenase (Sigma, St. Louis, MO, USA) and 0.25% trypsin in 10 mL PBS for 60 min at 37°C. The resulting cell suspension was filtered (44 μ m Millipore), centrifuged (1500 rpm, 10 min) and placed in a 35 mm culture dish. The purity of cultures was determined on the following day; 10 μ M, 0.05 mL AraC solution was added to the culture medium to remove fibroblasts and the medium was incubated for 4 days. The culture was plated on poly L-ornithine-covered 25 cm² flasks (2×10^5 cells per 5 mL) in an incubator with 5% CO₂ at 37°C. The culture was fed with Dulbecco modified Eagle (DME) medium (HyClone Laboratories, Inc, Logan, Utah USA) supplemented with 1% (v/v) antibiotics (10,000 U/mL penicillin G and 10 mg/mL streptomycin), 2 mM glutamine and 10% fetal calf serum (Biologic Industries, Kibbutz Beit Haemek, Israel). Cultures were maintained under standard culture conditions for about 2 weeks until a confluent monolayer was obtained. The identification of Schwann cells was verified using the S-100 staining method and the purity of the culture exceeded 95%.

Animals and experimental design

A total of 52 male Sprague–Dawley rats, weighing 250 to 300 g, were divided into seven groups. Group 1 (n

= 4) received 10-mm reversed autografts into their right sciatic nerves and served as a control. Groups 2 and 3 (n = 8 each) comprised 12-mm silicone conduits that underwent sham and ultrasonic stimulation, respectively. Groups 4 and 5 (n = 8 each) consisted of 12-mm PLGA conduits that received sham and ultrasonic treatment. Finally, groups 6 and 7 (n = 8 each) were comprised of PLGA conduits, the inner walls of which were seeded with Schwann cells; group 6 received sham treatment and low-intensity US was applied to group 7.

Fabricating PLGA conduits

A 20% solution (wt/wt) of polylactide-co-glycolide in an 85:15 monomer ratio (85:15 DL-PLGA, IV 0.9 to 1.2) (Invigor Biotechnology Inc., Taipei, Taiwan) was prepared in 1,4-dioxane reagent (Sigma). Conduits were formed by dipping a glass mandrel into PLGA solution, followed by immersion in 95% isopropyl alcohol. After air-drying, the polymer conduits were manually demolded from the glass mandrel. Lyophilization at dry ice temperature (−78 °C) yielded a polymer with a median pore size of 15 to 20 μ m. The PLGA conduits had the following dimensions: 1.6 mm i.d., 2.0 mm o.d. and length 12 mm. Conduits were stored in a dry environment.

Preparing conduit seeded with Schwann cells

Schwann cells were expanded for 8 weeks in culture and prepared for use. The conduits were sterilized by soaking in 70% alcohol for 30 min and rinsed with normal saline. The internal wall of the conduit was coated with 10% poly L-ornithine (Sigma) to promote the adherence of Schwann cells. The suspension of Schwann cells (3×10^5 cells/mL) was injected into the conduits. The volume of each conduit was approximately 20 μ L. Therefore, the seeding amount was around 6×10^3 cells per conduit. Cells were homogeneously seeded over the inner conduits by placing on a 5 rpm rotary deck for 20 min.

Surgical procedure

Animals were deeply anesthetized with sodium pentobarbital (30 mg/kg IP) throughout the surgical procedure. Surgery was conducted on the rat's right leg, under aseptic conditions. After an incision had been made in the skin, the sciatic nerve was exposed by making a muscle-splitting incision. An operating microscope (Leica Microsystems, Deerfield, IL) was used to divide the sciatic nerve near its origin, and a 10-mm nerve segment was excised with microscissors. In group 1, the autograft was reversed to prevent any branching of axons through the side branches during regeneration. In groups 2 to 7, the 12-mm prosthesis, PLGA or silicone conduits (Silastic, RX50, Dow Corning; 1.57 mm i.d., 2.41 mm o.d.) were interposed into the nerve gaps. The proximal nerve was anchored in the conduit by 9-0 nylon micro-

sutures. The distal end was then sutured into the other end of the conduit. Nerve stumps at both ends were sutured into the conduit to a length of approximately 1 mm. Hence, 10 mm of the nerve gap was left between two stumps. The wound was then closed in layers using 4-0 Dexon sutures. The animals were housed in temperature (22 °C)- and humidity (45%)-controlled rooms with 12-h light cycles; they had access to food and water ad lib. All procedures followed animal care and use committee of our university guidelines.

Ultrasound application

At 24 hours following surgery, the US stimulator (Therasonic 350, Electro-Medical Supplies (Greenham) Ltd., Wantage, Oxfordshire, UK) was applied around the incision site on the rat, using a probe with an active area of 5 cm². A total of 12 treatment sessions were given over a period of 2 weeks. Each treatment was at a frequency 1 MHz; with pulse duration of 2 ms, a pulse repetition rate (PRR) of 100 Hz, a duty cycle of 20% and an intensity of 0.2 W/cm² (SATP) for a treatment time of 5 min daily. The probe was gently applied near the incision site to prevent inflammation. Aquasonic gel was employed as a coupling medium before treatment. Groups 2, 4 and 6 received sham stimulations and underwent identical treatment, using a dummy transducer without ultrasonic output.

Histologic analysis

At 6 weeks following implantation, all animals were euthanized by methoxyfluorane overdose. The midconduits of the implanted grafts were harvested and histologically analyzed. The nerve grafts were immediately fixed in a cold buffered 3% glutaraldehyde solution. Nerve grafts were then washed in 0.1 mol/L phosphate buffer (Fischer Scientific, Fair Lawn, NJ) and divided into 2- to 3-mm segments to ensure precise localization. These segments were then postfixed in 1% osmium tetroxide (Polysciences, Warrington, PA), dehydrated in a graded series of ethanol solutions and finally embedded in spurs. The embedded nerves were cut to 5- μ m thickness and then stained with 1% toluidine blue, which did not stain PLGA.

All nerve sections were observed under a light microscope and photographs were taken using a digital camera (COOLPIX 995, Nikon Co., Tokyo, Japan). Analyses were conducted using an image analysis system (Image-Pro Lite, Media Cybernetics, San Diego, CA, USA) to determine the number and areas of individual myelinated axons. Additionally, the cross-sectional area of the whole nerve section was measured under 40 \times and 400 \times magnification. Three randomly selected fields with an area of 80 μ m \times 60 μ m in each nerve specimen were observed at a magnification of 400 \times , and the axons were counted. The numbers of

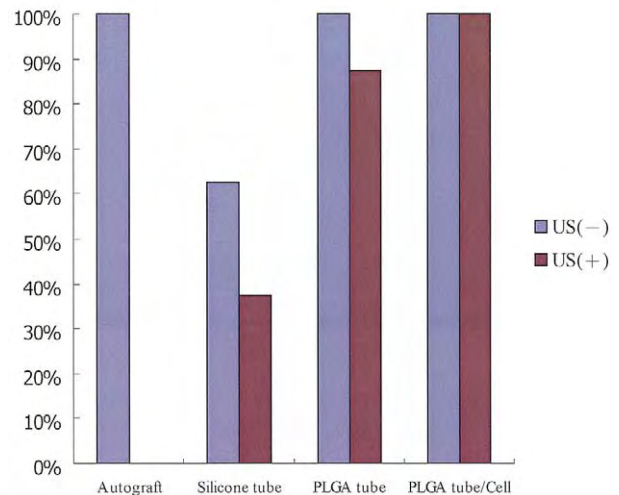


Fig. 1. Rates of success of regeneration of nerve across 10 mm gap.

axons were extrapolated by applying the area algorithm to estimate the total number of axons associated with each nerve. Moreover, the mean area of the axons for each nerve specimen was also determined.

All data were obtained and expressed as means \pm standard errors (SE). The control group (autografts) was compared with the experimental groups and the sham group was compared with the stimulation group. Statistical significance was determined by the Student's *t*-test.

RESULTS

Figure 1 presents the rates of successful nerve regeneration across the 10-mm gap at 6 weeks in all groups. Silicone conduits in groups 2 and 3 exhibited rather low rates of successful regeneration, 62.5% (5 of 8) and 37.5% (3 of 8), compared to those of PLGA conduits in groups 4, 5, 6 and 7, 100% (8 of 8), 87.5% (7 of 8), 100% (8 of 8) and 100% (8 of 8). Gross observation of the specimens revealed that a thin capsule of fibrous tissue grew and covered the implanted silicone conduit in group 2. Reactions of large foreign bodies on silicone conduits in the ultrasonic stimulation group, group 3, were observed with vast fibrous capsules covering the implanted silicone nerve conduits (3 of 8) (Fig. 2a). In groups 4, 5, 6 and 7, parts of the PLGA conduits were degraded, absorbed and decomposed into fragments. No obvious reactions of foreign bodies in the surrounding tissue were observed (Fig. 2b).

Histologic analysis

Figure 3a and b shows representative cross-sections of PLGA conduits seeded with Schwann cells in groups 6 (US-) and 7 (US+). Populations of fibroblasts, con-

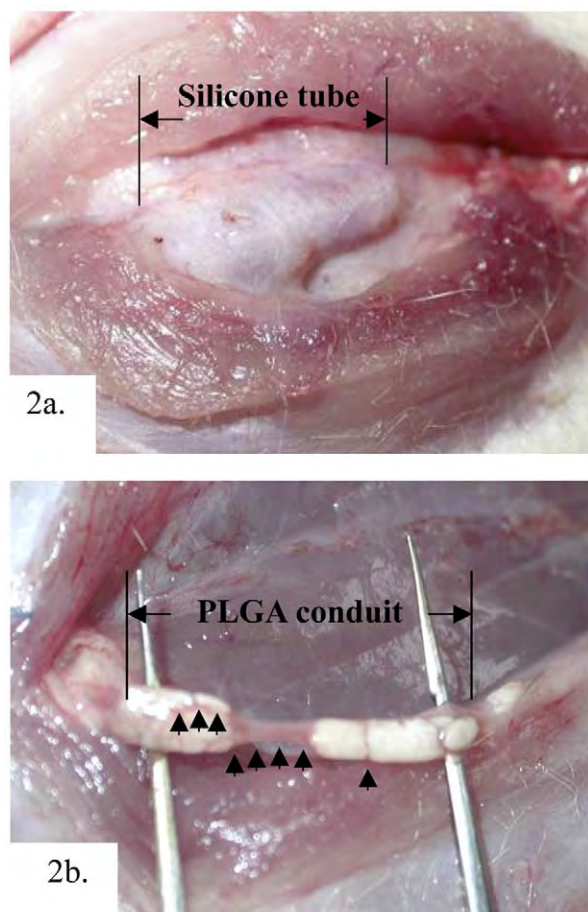


Fig. 2. Gross observation of specimens. (a) Silicone conduit with US+; the mass fibrous capsule was covered the implanted silicone conduits. (b) PLGA conduit seeded with Schwann cells and US+; some of the PLGA conduits were degraded and absorbed (arrow head); the wall of conduit was decomposed into fragments.

nective tissue and blood vessels invaded the PLGA conduits. Numerous Schwann cells were visible and some actively participated in myelination. The regenerated myelin sheaths of the injured nerves in group 6 (US-) were with smaller diameters and thinner than those in group 7 (US+). Some axons were myelinated with myelin sheaths (type A and B fibers) and some thinner ones were still unmyelinated (type C fibers). Moreover, as the disuse atrophy of muscle bundle diverged, the number of nuclei increased. Fatty infiltration and muscle fibrosis were also observed (Fig. 4a, b).

In the middle of regenerated nerve, the application of ultrasound to PLGA conduits seeded with Schwann cells (group 7) demonstrated statistically more myelinated axons than the sham group (group 6). In particular, group 7 exhibited the most axons, even more than autografts. Notably, the silicone conduits under ultrasonic

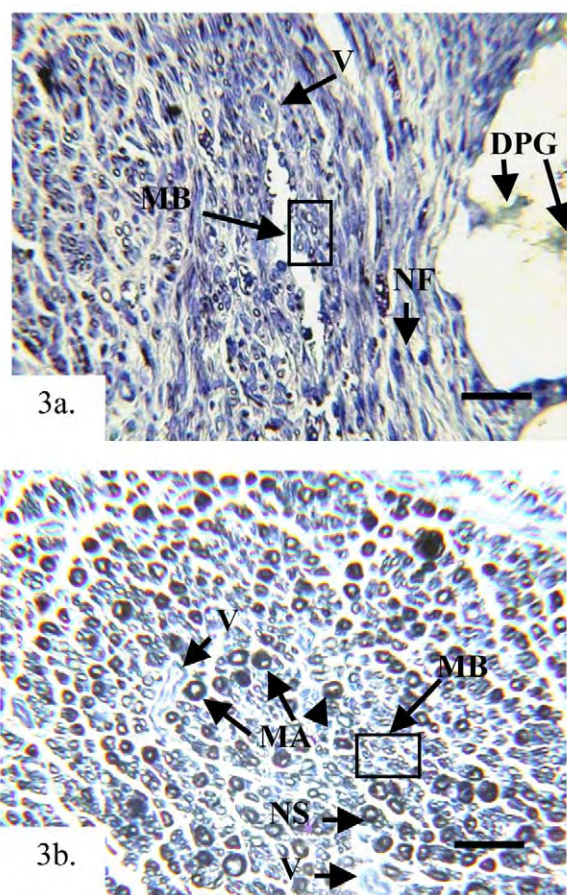


Fig. 3. Transverse sections of the sciatic nerves from a medial graft to the injury. (a) PLGA conduit seeded with Schwann cells and US-. (b) PLGA conduit seeded with Schwann cells and US+. V = vessel; MA = type A myelin fibers; MB = type B myelin fibers; NS = nucleus of Schwann cell; NF = nucleus of fibroblast; DPG = degraded PLGA. Scale bar = 20 μ m.

stimulation (group 3) had statistically fewer axons than the sham group (group 4) (Fig. 5). The mean area of the axons followed a similar pattern; the US-stimulated implant had statistically higher values than did the sham control in the PLGA conduits (groups 5 and 7), except in the case of the silicone conduits (group 3) (Fig. 6).

DISCUSSION

Crisci and Ferreira (2002) found that low-intensity pulsed US has accelerated the regeneration of a peripheral nerve following neurotomy. They suggested that the numerous thick fibers in the nerves of animals that were stimulated with US were generated because of the stronger activity of the Schwann cells, accelerating the recovery of myelin sheaths. An *in vivo* sciatic nerve conduit model system of the rat is used and histologically analyzed to yield more insight into the possibility of US treatment affecting the seeded Schwann cells.

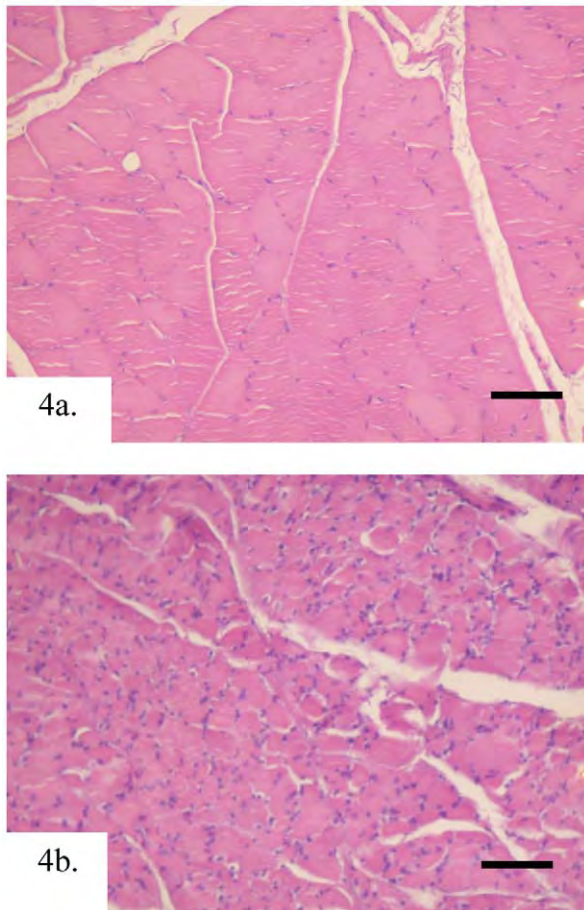


Fig. 4. Transverse sections of gastrocnemius muscle in (a) normal muscles, and (b) PLGA conduit group. Scale bar = 40 μm .

The rates of successful nerve regeneration of the PLGA groups differed considerably from those of the silicone groups after 6 weeks. However, no differences between the stimulated PLGA and the sham PLGA groups were observed, regardless of whether the Schwann cells were seeded. Mickinnon and Dellon (1990) indicated that hollow conduits cannot achieve results similar to those of autografts (gap > 10 mm in rats). In other words, a hollow conduit has the chance to bridge the gap which is less than 10 mm. In addition, the permeability of the porous PLGA conduit is considered to be responsible for the improved regeneration over the impermeable silicone tubes (Gregory and Evans 2000). Therefore, regardless of whether US was applied, the PLGA conduit could bridge the 10-mm nerve gap at 6 weeks.

Stimulation of silicone conduits by US detrimentally influenced nerve regeneration, as compared with that of the sham group. Gross examination of silicone conduits that underwent ultrasonic treatment showed that 3 of 8 specimens were covered with massive fibrous tissues at 6

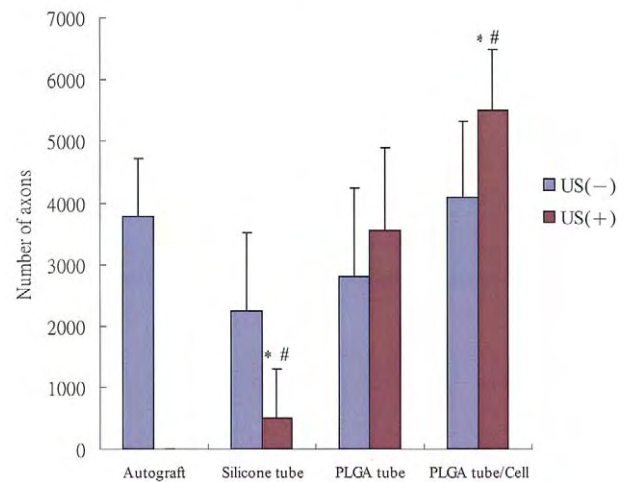


Fig. 5. Number of axons at the midconduit of the seven groups after 6 weeks. Error bars represent means \pm SE. * Significantly different from the sham group; # significantly different from the autograft group ($p < 0.05$).

weeks. The implanted PLGA conduits exhibited degradation but the lumens remained undeformed.

The various effects of US in conduits made of PLGA and silicone rubber may be attributed to the differences between the characteristics of these two materials. Nonbiodegradable materials, such as silicone rubber, frequently cause foreign body reactions (Lanza et al. 2000). However, another important reason for such reaction may have been the difference between the acoustic impedance of these two materials. Carstensen (1986) and Holland and Apfel (1990)

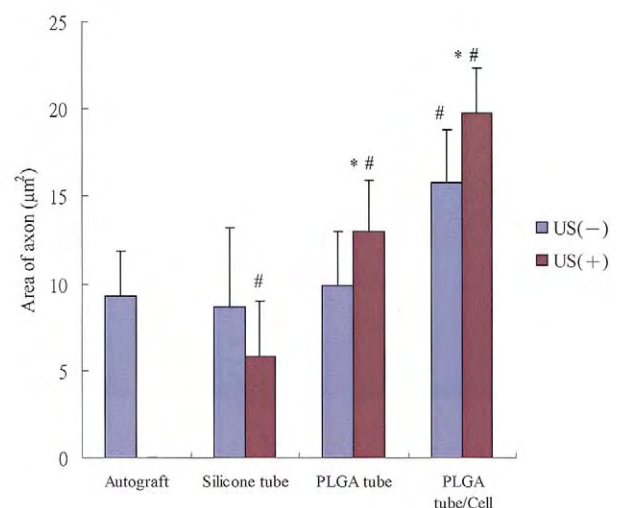


Fig. 6. Area of axons (μm^2) at the midconduit of seven groups after 6 weeks. Error bars represent means \pm SE. * Significantly different from the sham group; # significantly different from the autograft group ($p < 0.05$).

noted the potential hazard of collapse cavitation caused by generated standing waves that are formed by the interference of US waves that are reflected at the high-impedance interface (for example, at the mineralized matrix of the bone). Wells (1977) also stated that differences between acoustic impedances of tissue, such as those where a mineralized matrix of intact bone tissue is surrounded by periosteum, result in the reflection of the US beam and subsequent interference can generate peaks in US intensity. The nonbiodegradable silicone conduits may exhibit high impedance when the US is applied, forming collapse cavitation and causing serious foreign-body reactions. The biodegradation and the porosity of the biodegradable PLGA conduits may reduce hazardous reflections and prevent the formation of collapse cavitation and the subsequent reactions of foreign bodies.

The histologic analysis data revealed that ultrasonically stimulating the PLGA group resulted in a statistical increase in the number and area of regenerated axons at the midconduit portion of the implanted grafts seeded with Schwann cells. Therefore, the nonthermal effects of applied US probably stimulated the seeded Schwann cells within PLGA conduits and improved the inflamed milieu. These prompt effects were consistent with the positive effect of US on neurotomy in rats, as reported by Crisci and Ferreira (2002). Additionally, the reversal of this positive effect using a silicone conduit was demonstrated. Incorporating ultrasonic stimulation and Schwann cell seeding therefore appears to constitute a potentially improved approach to developing a tissue-engineering conduit for regenerating peripheral nerves.

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Ultrasound Accelerates Functional Recovery after Peripheral Nerve Damage

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OBJECTIVE: Axonal injury in the peripheral nervous system is common, and often it is associated with severe long-term personal and societal costs. The objective of this study is to use an animal model to demonstrate that transcutaneous ultrasound can accelerate recovery from an axonotmetic injury.

METHODS: The sciatic nerve of adult male Lewis rats was crushed in the right midthigh to cause complete distal degeneration of axons yet maintain continuity of the nerve. Beginning 3 days after surgery, various transcutaneous ultrasound treatments or sham treatments were applied 3 days per week for 30 days to the crush site of rats that were randomly assigned to two groups. In the preliminary experiments, there were three animals in each ultrasound group and two control animals. In the final experiment, there were 22 animals in the ultrasound group and 20 animals in the control group. Recovery was assessed by use of a toe spread assay to quantify a return to normal foot function in the injured leg. Equipment included a hand-held transducer that emitted continuous-wave ultrasound. The most successful ultrasound protocol had a spatial peak, time-averaged intensity of 0.25 W/cm^2 operated at 2.25 MHz for 1 minute per application.

RESULTS: Rats subjected to the most successful ultrasound protocol showed a statistically significant acceleration of foot function recovery starting 14 days after injury versus 18 days for the control group. Full recovery by the ultrasound group occurred before full recovery by the control group.

CONCLUSION: Transcutaneous ultrasound applied to an animal model of axonotmetic injury accelerated recovery. Future studies should focus on identification of the mechanism(s) by which ultrasound creates this effect, as a prelude to optimization of the protocol, demonstration of its safety, and its eventual application to humans. (Neurosurgery 48:1136–1141, 2001)

Key words: Functional recovery, Peripheral nerve injury, Therapeutic ultrasound

Peripheral neuropathy caused by injury or disease is a common clinical problem. It often debilitates by producing significant motor and sensory deficits as well as pain and other unpleasant sensations (14). Recovery, when it occurs, is often slow and incomplete, leading to personal hardship for the patient and significant costs to society at large (5, 13). The severity or grade of a peripheral nerve injury is one of the most important determinants of recovery (9, 11). Mild to moderate acute injuries and chronic entrapment neuropathies, the most common of which is carpal tunnel syndrome

involving the median nerve in the hand, usually result in demyelination of the nerve with preservation of the axons. Recovery from this neurapraxic grade of injury requires remyelination of axons. Acute and chronic injuries of greater magnitude result in degeneration of nerve fibers distal to the site of trauma (an axonotmetic grade of injury), and recovery requires not only remyelination but also axonal regeneration. Examples of such injuries include severe grades of carpal tunnel syndrome and diabetes as well as some types of trauma. If the cellular and extracellular components that form

Ultrasound Accelerates Axonal Healing

a suitable substrate for axonal regeneration are available, as in a crush injury, then nerve fibers regenerate at an average rate of approximately 1 mm per day (9, 11). For proximal injuries that require axons to traverse long distances before they reach target muscles or sensory receptors, recovery of function can take up to 2 years (13).

Current treatments for disabling nerve injuries often involve surgical decompression for entrapment neuropathies and surgical exploration and repair after traumatic nerve injuries (9, 11, 13). To date, trials of drugs for peripheral neuropathies, including various neurotrophic factors, have been unsuccessful (19). Despite advances in the medical and surgical management of peripheral nerve injuries, recovery is often incomplete. Major impediments to a full recovery include the long delay and imprecision in successful reinnervation of motor and sensory target structures (8). Development of new treatments to accelerate and improve the recovery process would provide clinical benefits. In this study, we demonstrate that low-intensity therapeutic ultrasound can accelerate functional recovery in an animal model of a completely crushed peripheral nerve.

MATERIALS AND METHODS

Technical approach

Surgical protocol

The sciatic nerve of rats was crushed in the right midthigh by use of a protocol known to cause complete distal degeneration of axons yet maintain the continuity of the nerve (2, 4). In brief, adult male 200- to 300-gm Lewis rats (Charles River Breeding Laboratories, Portage, Canada) were anesthetized with intraperitoneal pentobarbital (50 mg/kg). Aseptic microsurgical techniques were used to make a longitudinal incision along the lateral thigh and upper portion of the leg and expose approximately 15 mm of the sciatic nerve on the right side. The sciatic nerve was then crushed forcefully three times, for 10 seconds per crush, with fine smooth forceps at a point 5 mm distal to the sciatic notch. The muscle fascia was then reapproximated and the skin incision closed with interrupted sutures. After this surgical procedure, the animals were assigned randomly to two groups, one to be subjected to ultrasound, the other to act as controls. In the initial experiments with several ultrasound protocols, there were two control animals and three animals in each ultrasound group. In our final experiment, there were 22 control animals and 20 animals in each ultrasound group. Because animals were killed at various time points during this experiment, the number of animals in the study became smaller as the final experiment progressed, as discussed in the Results section. In all cases, the animals were anesthetized before they received ultrasound or sham ultrasound.

Ultrasound protocol

Continuous-wave ultrasound with a variety of spatial peak, time-averaged intensities, as well as a variety of frequencies and durations (described in the Results section), was centered at the crush site. Ultrasound was applied transcutaneously with a V304 handheld transducer (Parametrics, Inc., Waltham, MA) driven by a class B amplifier (ENI, Rochester, NY) that was controlled by an HP3312A programmable function generator (Hewlett-Packard, Avondale, PA) (Fig. 1). Coupling of ultrasound from the transducer into the animal was achieved by submerging the animal's lower extremities and the transducer in a tepid water bath maintained at 27°C with the transducer held 2 to 3 cm from the surgical site. The transducer was moved along the nerve with a motion of approximately 1 Hz, such that the center of the transducer moved approximately 5 mm proximal and 10 mm distal to the crush site. Because of the size of the transducer, approximately 1.75 cm of the nerve proximal and distal to the crush site was insonified. Beginning on the 3rd postoperative day, this procedure was performed for 1 minute, three times per week for 4 weeks. Control animals underwent the same procedure but with an inactive ultrasonic device.

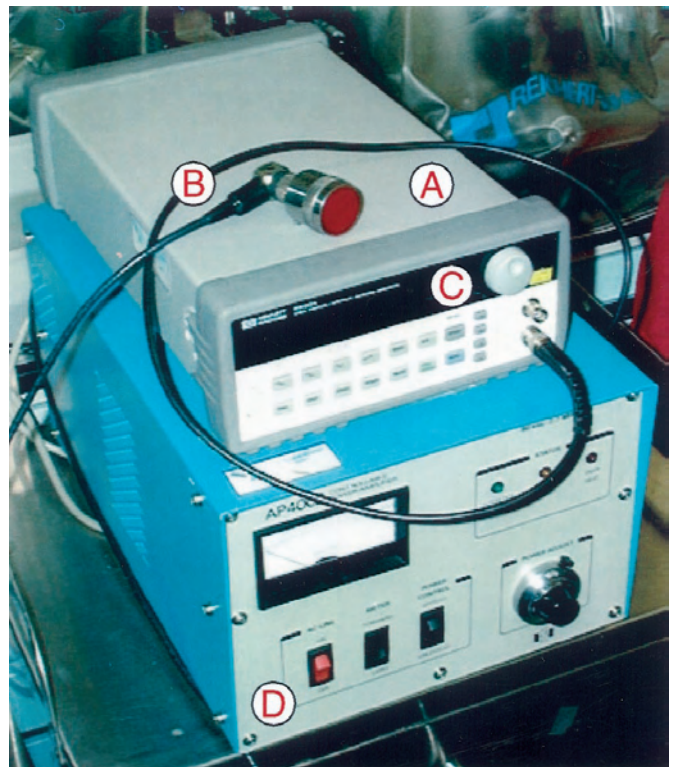


FIGURE 1. Ultrasound equipment. A, transducer; B, waterproof B&C cable; C, function generator; D, amplifier. The red part of the transducer measures 2.54 cm in diameter and is the source of a spatially uniform acoustic field.



FIGURE 2.
Application of dye
to rear feet of rat.

Toe spread assay

Recovery of function was assessed by quantification of toe spread (3) one to three times per week. In brief, both hind limbs of each of the experimental and control animal were dipped in water-soluble blue ink (Fig. 2), and each animal was allowed to walk down a track lined with white paper, leaving its hind prints on the paper (Fig. 3). If the toe spread assay and application of ultrasound occurred on the same day, the assay was performed first.

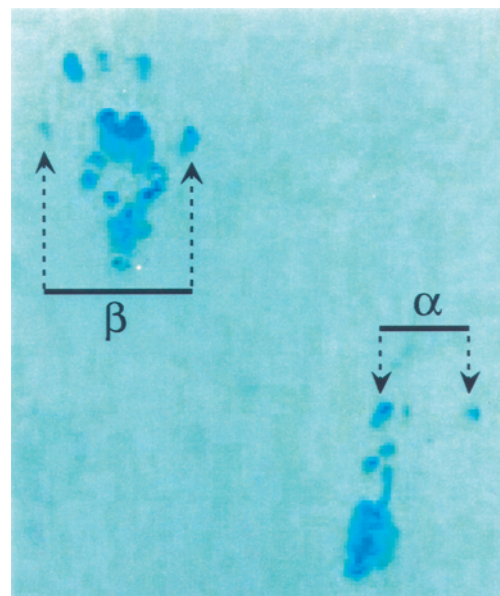
The paper was then coded by animal number, with no reference to experimental group, which allowed unbiased measurement of the walking track by one of the authors (DAL). The distance between the first and fifth toes was measured, and a toe spread index was calculated (Fig. 4). The toe spread index for each experimental group was compared with that of the control group, which did not receive ultrasound.

Statistical analysis

Using Statistica software (StatSoft, Tulsa, OK), we applied an unpaired, two-tailed Student's *t* test to the summary number of each group of results to analyze whether there was a statistically significant difference in recovery of foot function between the ultrasound and control groups. The same statistical test was applied to the experimental results for each day of interest. A *P* value of <0.05 was considered statistically significant.

RESULTS

The results of our first experiment with several ultrasound protocols are shown in Figure 5 with a description of each pro-



$$\text{Toe Spread Index} = (\alpha/\beta) \times 100$$

FIGURE 4. An example of the toe spread index used to assess recovery. The toe spread index is given by the geometric distance (α) between the first and fifth toes of the injured right rear leg of a given rat, divided by the distance (β) between the first and fifth toes of its uninjured left rear leg, scaled to percentage.

tol. The results show a statistically significant acceleration of foot function recovery in two ultrasound protocols as well as an earlier recovery of full function. The second set of experiments used the most successful protocol shown in Figure 5, with a frequency of 2.25 MHz and a spatial peak, time-averaged intensity of 0.25 W/cm² applied for 60 seconds three times per week. The results (Fig. 6) demonstrate a statistically significant acceleration of foot function recovery, which began 14 days after the crush injury for the experimental group versus 18 days for the control group; the experimental group also experienced earlier recovery of full function.

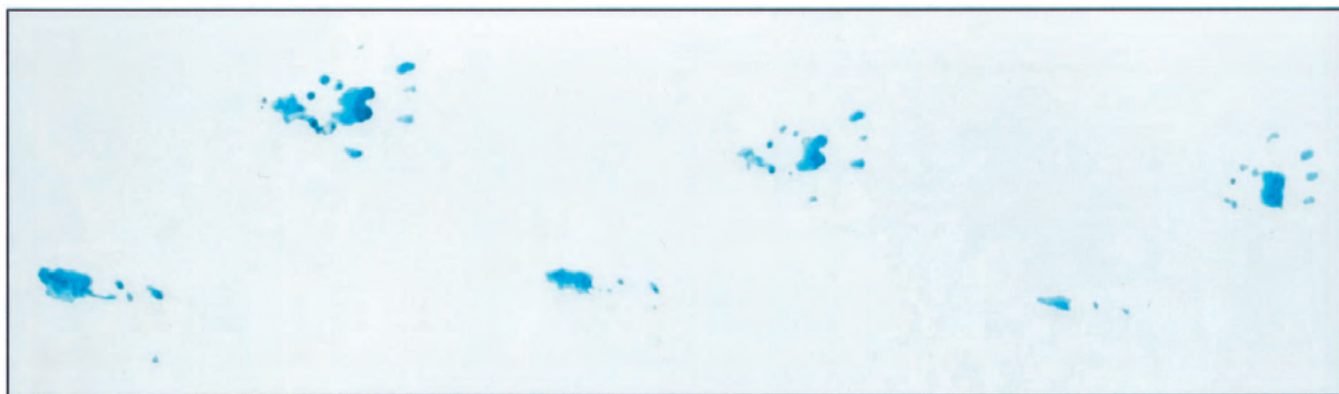


FIGURE 3. Sample footprint patterns showing footprints of uninjured foot (top) and injured foot (bottom).

DISCUSSION

Ebenbichler et al. (6) demonstrated in clinical trials that ultrasound can improve symptoms as well as median nerve conduction velocity in patients with a neurapraxic grade of injury. In a rat model of a more severe injury, which involved a partial crush lesion that produced both demyelination and axonal decay, Hong et al. (10) demonstrated that ultrasound can accelerate recovery of normal conduction velocity. Motivated by these results, we applied ultrasound to an even more severe grade of peripheral nerve injury, i.e., a complete crush injury that resulted in complete degeneration of myelin and axons distal to the injury site. The results in Figure 5 demonstrate that the acoustic protocol of Hong et al. (10) (Protocol 2) did not improve functional recovery in this rat model of a complete axonotmetic injury. However, two other ultrasound protocols improved functional recovery. The results plotted in Figure 6, with their greater statistical power, confirmed the ability of ultrasound to accelerate recovery from a complete axonotmetic grade of injury.

By what acoustic and biological mechanisms may ultrasound create this beneficial biological response? Ultrasound interacts with tissue via local heating, cavitation, and/or radiation pressure (12). In principle, ultrasound Protocols 1, 2, and 4 were designed to engender the same local heating ($<1^{\circ}\text{C}$ by use of the formulas discussed by Mourad [12]) in tissue. Because ultrasound Protocols 3 and 4 produced accelerated recovery, these preliminary results suggest that ultrasound-induced heating is not the acoustic mechanism that causes the observed biological effect. Cavitation is unlikely, given the low intensity of the ultrasound and the high threshold for cavitation in tissue (12). Therefore, radiation pressure is the remaining candidate for the acoustic mechanism by which ultrasound accelerates recovery.

As for biological mechanisms, ultrasound may enhance recovery of nerve function by modulating certain cellular and molecular responses that are involved naturally in the healing process. This is a reasonable hypothesis, because ultrasound has been demonstrated elsewhere to accelerate both the degeneration and regeneration phases of flesh wound healing, as reviewed by Williams (15) and Mourad (12), as well as the regeneration phases of bone fracture healing (16) and healing of severed tendons (7). Accelerated protein production is a common theme of many of these studies, although increased macrophage activity (17) and angiogenesis (18) also have been observed. Therefore, candidate-modulated processes for additional investigation in the present context include axonal and myelin degeneration, axonal and myelin regeneration, enhancement of the specificity of axonal targeting, enhancement of axonal spouting at the target muscle, and modulation of specific cytokines and/or trophic factors (8). It is well known that the natural processes of healing in damaged peripheral nerves can be modulated. For example, a peripheral nerve regenerates more rapidly after a second injury because of the "conditioning lesion" effect (11). In addition, recent work (1) demonstrates that the speed and accuracy of motor axonal regeneration can be accelerated by direct electrical stimulation proximal to the injury site.

CONCLUSION

We have observed an improvement in the rate of recovery in vivo in an animal model of an axonotmetic grade of peripheral nerve injury after the transcutaneous application of therapeutic ultrasound to the injury site. Therefore, ultrasound eventually may prove useful in clinical practice to accelerate and improve functional recovery after a severe grade of peripheral nerve injury that requires axonal regeneration.

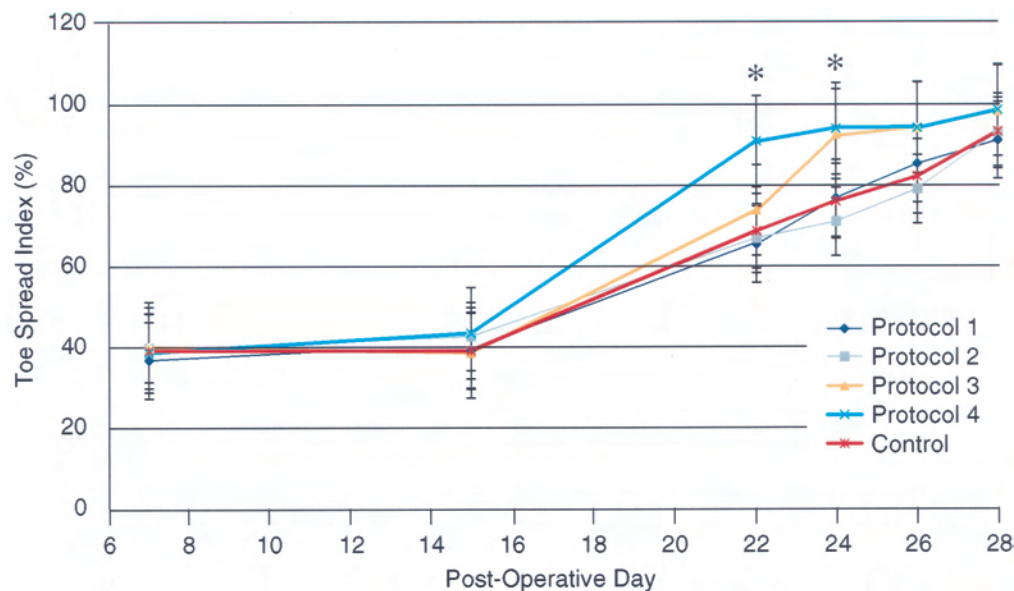


FIGURE 5. Graph of toe spread index versus postoperative day for four different ultrasound protocols ($n = 3$ for each protocol) and a control group ($n = 2$). The ultrasound protocols are described by their spatial peak, time-averaged intensity (W/cm^2), frequency (MHz), and duration of application. **Protocol 1**, 5 W/cm^2 , 1.0 MHz, 6 seconds; **Protocol 2**, 0.5 W/cm^2 , 1.0 MHz, 60 seconds; **Protocol 3**, 0.25 W/cm^2 , 1.0 MHz, 60 seconds; **Protocol 4**, 0.25 W/cm^2 , 2.25 MHz, 60 seconds. Statistical analysis of the entire data set showed

statistically significant differences in the results ($P < 0.05$). The difference between Protocol 4 and the control group at postoperative Day 22 is statistically significant ($P < 0.02$). The difference among each of Protocols 3 and 4 and the control group at postoperative Day 24 also is statistically significant ($P < 0.05$).

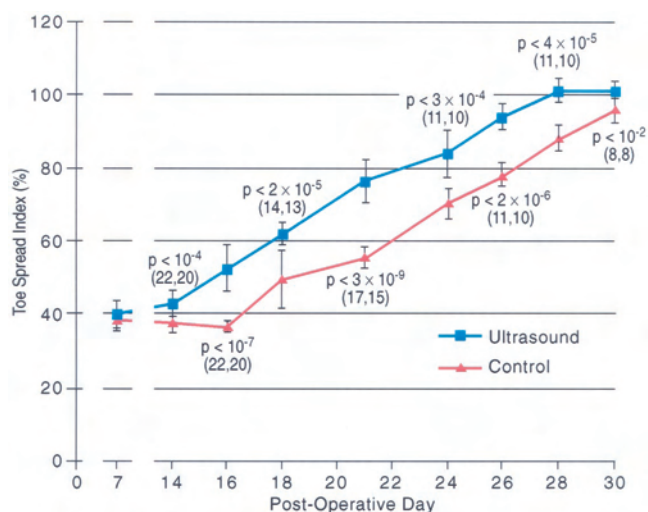


FIGURE 6. Graph of toe spread index versus postoperative day for ultrasound-treated and control animals. The most successful protocol demonstrated in Figure 5 was used. Statistical analysis of the entire data set showed a statistically significant difference between the two groups over time ($P < 5 \times 10^{-9}$). The statistically significant difference at relevant days is noted on the graph, as well as the total number of animals in the ultrasound-treated and control groups.

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COMMENTS

All experimental attempts to improve regeneration, especially functional nerve regeneration, are a pleasure to review, especially when the experiment(s) are as well done as the one reported in this article. Using a crushed, axonotomically injured nerve, which in a rat regenerates extremely well, small but significant differences are demonstrated in the ultrasound-treated limbs as opposed to the control limbs. These small differences were in the toe spread index compared at 7, 14, 16, 18, 21, 24, 26, 28, and 30 days postoperatively. The treatment administered was ultrasound for any 1 minute, 3 times per week for 4 weeks.

It is very difficult to demonstrate meaningful differences, especially in useful regeneration in the rat, which will recover an amazing amount of function even under circumstances much more adverse than those described in this experiment. Such injuries include those that would clearly be neurotmetic in higher animals such as the primate or human. Thus, in the area of nerve research, the rat is a much better research model than studying comparative treatments with regard to working out basic processes. Therefore, it is important for these investigators to move their work up the phylogenetic scale to determine whether significant differences can be corroborated by well-planned electrophysiological and anatomic end points in higher

animals such as primates. This is especially important because ultrasound treatment, if it proves efficacious, would be relatively simple to administer in the injured limb and moreover should cause no deleterious side effects. The authors present a method of treatment worthy of further research.

David G. Kline
New Orleans, Louisiana

This interesting article provides preliminary data strongly suggesting that intermittent application of ultrasound energy to an injured nerve with Wallerian degeneration can accelerate the recovery of nerve function. The authors found statistically significant shortening of time to recovery of nerve function as demonstrated by improving toe spread.

One of the major problems in nerve repair has been the slow regrowth of recovering axons, which seemingly is limited to about 1 mm per day and hitherto has largely been unaffected by application of growth factors. The long delay, causing distal reinnervation, leads to atrophy of the target muscles and significant deterioration in the degree of recovery. Any factor that could increase the rate of axon regeneration or maturation would be most useful. The means by which ultrasonic energy may be able to affect nerve recovery is uncertain, as the authors point out.

I hope that the authors will follow up this study with more detailed investigation of this phenomenon, including histological studies of the nerves with axon counts, myelination indexes, and analysis of Schwann cell activity. I look forward to future reports of this encouraging work.

John E. McGillicuddy
Ann Arbor, Michigan

The authors have developed a protocol of transcutaneous ultrasound application to the sciatic nerve in a rat model after a crush lesion to this nerve. The results of this treatment were compared with the results in a group of control animals. During the 30 days after injury, the animals were regularly examined by a functional test that quantifies toe spreading. In the early phase of nerve regeneration, the ultrasound animals did better than the control animals. At the end of the examination period (30 days after injury), however, this difference had almost disappeared.

Although it is unknown how ultrasound influences peripheral nerve regeneration, these experiments lead me to the conclusion that there is such an influence, at least in the sciatic nerves of rats.

Before ultrasound may be applied in humans, it should be tested in primates. If the results of these rat experiments were found to be transferable to primates, it would mean that functional recovery after an axonotmetic nerve injury is accelerated by transcutaneously applied ultrasound but that the final result is not superior as compared with those who do not receive this treatment. All of this is speculation that awaits proof.

Hans-Peter Richter
Ulm, Germany

In this article, Mourad et al. present data that they believe supports the conclusion that ultrasound treatment accelerates recovery of function in peripheral nerves in an animal model of crushed peripheral nerve. The mechanism of this effect is the subject of speculation but remains unknown. I need more than this small project to convince me.

The mechanism of sciatic nerve injury used in this experiment is not well controlled for uniformity of injury, for as the authors state, "The sciatic nerve was . . . crushed forcefully three times, for 10 seconds per crush, with fine smooth forceps at a point 5 mm distal to the sciatic notch." This mechanism certainly leaves room for variation in the amount of crushing force exerted by the operator. It is thus possible that the control group received a slightly more severe overall injury than the ultrasound-treated group. If this was the case, then the interpretation of *Figure 5* would be different. That is, it could be stated that both groups recovered at a simultaneous rate between Days 16 and 28 postinjury. The difference in the control and treated curves could be that the control group received a slightly more severe injury and that the groups of animals were simply not followed long enough for the control animals to reach 100% toe spread index. It is also worrisome that the number of animals in the treated group dropped by 50% and those in the control group decreased by 64% during the 30-day duration of the experiment.

Crushing injuries to nerves, chronic entrapment neuropathies, and metabolic peripheral neuropathies have very different anatomic pathophysiologies, clinical presentations, and clinical outcomes. Much more work needs to be done to demonstrate conclusively that ultrasound treatment makes a difference in any of these entities in the animal and human models before I will become enthusiastic about recommending its use.

Suzie C. Tindall
Atlanta, Georgia



ABSTRACT: Though the use of ultrasound for the treatment of carpal tunnel syndrome (CTS) or compression neuropathy has been described, its effect remains controversial. A test model of acute CTS was developed using rabbits. Acute median nerve compression was induced by the infusion of saline into the carpal tunnel under general anesthesia to elevate the intracarpal pressure. A reduction in the compound muscle action potential (CMAP) amplitude of the abductor pollicis was noted after intracarpal pressure increased. To investigate the efficacy of ultrasound in acute CTS, rabbits with acute median nerve compression were divided into 3 groups (10 each) and ultrasound was applied at different intensities to each group as follows: 1.5 W/cm² to group 1; 0.2 W/cm² to group 2; 0.0 W/cm² (sham) to group 3. A total of 10 treatment sessions were given over a period of 2 weeks. Following ultrasound application, the CMAP amplitudes showed significant improvement in group 1 compared to the other two groups ($P < 0.05$), indicating facilitated recovery from acute CTS in this pressure-induced median nerve compression rabbit model. The benefits of ultrasound application in a clinical setting must be verified by further clinical trials.

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ULTRASOUND THERAPY FACILITATES THE RECOVERY OF ACUTE PRESSURE-INDUCED CONDUCTION BLOCK OF THE MEDIAN NERVE IN RABBITS

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Although acute-onset carpal tunnel syndrome (CTS) is uncommon, it may occur after trauma, such as Colles or carpal bone fracture, with other rheumatological, hematological, or endocrine disorders, and during pregnancy.³⁴ It has been suggested that acute CTS is caused primarily by increased intracarpal pressure that eventually blocks blood flow to the median nerve. Some evidence supports this hypothesis.³⁴ Cobb and colleagues⁷ suggested that the carpal tunnel acts as a compartment. Others^{21,35} confirmed that pressure in the carpal tunnel is increased in certain patients with CTS, and that this pressure decreases when the transverse carpal ligament is released.^{16,22,23}

Ultrasound treatment has been proposed for the early conservative treatment of CTS. The results of

two clinical trials have been published,^{11,24} but the results were contradictory. The subjects in the two studies differed, however, as did the dosage and method of ultrasound application. Ultrasound has a thermal and nonthermal effect. The former involves elevating tissue temperature, whereas the later induces media motion.^{6,10,20,38} If acute CTS is caused by ischemia of the median nerve due to elevation of intracarpal pressure, ultrasound therapy to increase blood supply within the tissue and thus accelerate nerve regeneration²⁰ is a plausible treatment option. This study was therefore undertaken to develop in rabbits an acute pressure-induced median neuropathy model of human acute CTS, and to examine in this model the effect of ultrasound treatment.

MATERIALS AND METHODS

Induction of Acute CTS. We used 30 New Zealand White rabbits over 4 months old and weighing 3.0–3.3 kg. Experiments were performed on one forelimb. The animals were raised under identical conditions. Anesthesia was induced by the intramuscular injection of ketamine hydrochloride (50 mg/kg) and xylazine (10 mg/kg), and, if necessary, an addi-

Abbreviations: CMAP, compound muscle action potential; CTS, carpal tunnel syndrome

Key words: animal model; carpal tunnel syndrome; median neuropathy; treatment; ultrasound

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tional dose was used for maintenance. The hair of the right forelimb was shaved with the rabbits lying on a blanket maintained at 38°C. After positioning the wrist, a 20-gauge intravenous catheter with a diameter of 1.1 mm and length of 45 mm was inserted into the carpal tunnel. The tip of the catheter was then connected to a pressure transducer (Marquette patient monitoring system SOLAR 8000, Marquette Medical Systems, Milwaukee, Wisconsin) that monitored carpal tunnel pressure. Heated sterile normal saline (36°C) was artificially infused into the distal carpal tunnel to elevate intracarpal pressure using a 21-gauge syringe (diameter, 0.8 mm; length, 32 mm) attached to an infusion pump. After inserting the catheter and syringe, the pressure transducer was calibrated to zero.

The target pressure (see later) was reached within 5 min and maintained within an error range of ± 5 mmHg. After reaching the desired pressure, the catheter and the syringe were removed to decrease carpal tunnel pressure by passive diffusion.

Electrophysiological Measurement. The amplitude and latency of the compound muscle action potential (CMAP) of the abductor pollicis were measured using an 8-mm-diameter silver chloride disk type of surface electrode. Latency was measured from the stimulus artifact to the initial take-off point, and the amplitude was measured from peak to peak.

The median nerve was stimulated proximal to the carpal tunnel. A subdermal needle electrode (model number 54516; Medelec, Old Woking, Surrey, United Kingdom) was used for stimulation. The cathode was placed 4 cm proximal to the active electrode using a compass, and stabilized by subdermal insertion. A rectangular pulse of 0.1-ms duration was delivered. Filters were set at 10 Hz and 10 KHz, sensitivity was 1–10 mV per division, and sweep speed was 1 ms per division. Temperature was measured using a digital needle thermometer, and maintained between 34–36°C. All subjects were examined using a Mystro electromyography machine (Medelec).

The same electrodes were used to minimize variability in measuring CMAP, and the stimulation and recording site were marked with indelible ink. All electrophysiological measurements were performed before ultrasound application to avoid thermal effects.

Study Design. Acute CTS was induced at a pressure of 100 mmHg, which was maintained for 4 h. This pressure was selected based on the results of a pilot study in 16 animals, in which an approximately 50%

reduction in CMAP amplitude was observed 2 days after induction.

Intertrial variability of the CMAP amplitude in individual rabbits (determined for 10 rabbits) was 14.8%, when animals were tested twice at an interval of 2 days. Acute CTS was operationally defined as a CMAP amplitude reduction of more than 15% of the initial value 2 days after induction.

In the present study, 30 rabbits with acute CTS were equally distributed to three treatment groups. Group 1 received an ultrasound power output of 1.5 W/cm² (thermal dose), group 2 received 0.2 W/cm² (nonthermal dose), and group 3 received 0.0 W/cm² (sham control). One session consisted of ultrasound application for 5 min, and a total of 10 sessions (5 sessions per week for 2 weeks) was given. Acute CTS was induced only in the right forelimb, and the animals were allocated to groups according to the induction sequence.

Ultrasound Application. Ultrasound was applied to the volar surface of the carpal tunnel with a stroking technique with a Sonoplus 590 (Enraf-Nonias, Delft, The Netherlands) using a 0.5 cm² surface area probe and 3.0 MHz output in continuous mode. Power output was periodically calibrated using an ultrasound power meter. Aquasonic gel was used as a coupling medium.

Outcome Assessment. The effect of treatment was evaluated electrophysiologically. The differences in recovery of CMAP compared to baseline (initial value before induction) in the three different treatment groups was observed at 2 days, 1 week, and 2 weeks after induction of acute CTS. The mixed random effect model was used for statistical analysis to study differences in terms of treatment group and time.¹⁹ SAS version 6.12 (SAS Institute, Cary, North Carolina) was used for statistical calculations.

Six median nerves from each group were extracted for semiquantitative histological evaluation. The percentages of degenerated myelinated fibers among the total number of myelinated fibers were determined microscopically at $\times 400$ in semithin sections. The degree of tissue damage and inflammation around the carpal tunnel were also compared.

RESULTS

Acute CTS was induced in 30 rabbits at a pressure of 100 mmHg and with a duration of 4 h. The baseline amplitudes and latencies (prior to induction) of the CMAP for each group were 13.0 ± 4.7 mV and 2.40 ± 0.17 ms in group 1, 13.1 ± 5.4 mV and 2.50 ± 0.23 ms in group 2, and 12.6 ± 5.1 mV and 2.49 ± 0.17 ms in

Table 1. Comparison of median nerve CMAPs among the groups.†

		Week			<i>P</i> value (groups)*		
Variable	Baseline	0	1	2	1 and 2	2 and 3	3 and 1
Amplitude (% control)							
Group 1	100	43.6 ± 12.0	64.6 ± 18.0	85.0 ± 22.7	0.0036	0.5791	0.0006
Group 2	100	41.2 ± 10.1	52.5 ± 10.6	63.1 ± 13.4			
Group 3	100	43.2 ± 20.0	50.8 ± 18.1	55.9 ± 16.3			
<i>P</i> value (times)*		0.0001	0.0003	0.0010			
Latency (ms)							
Group 1	2.40 ± 0.17	2.45 ± 0.28	2.44 ± 0.18	2.45 ± 0.21	0.1832	0.8355	0.1246
Group 2	2.50 ± 0.23	2.51 ± 0.56	2.50 ± 0.36	2.48 ± 0.22			
Group 3	2.49 ± 0.17	2.52 ± 0.11	2.50 ± 0.13	2.51 ± 0.20			
<i>P</i> value (times)*		0.5887	0.8105	0.9608			

†Applied dose of ultrasound therapy: group 1 (1.5 W/cm²); group 2 (0.2 W/cm²); and group 3 (0.0 W/cm²).

**P* values were obtained from random-effects model analysis. *P* value (groups): comparison between groups (group effect); *P* value (times): comparison between times (time effect).

group 3, respectively. There were no significant differences among the three groups.

Two days after induction (0 week), the CMAP amplitude decreased to 43.6 ± 12.0% of the baseline amplitude in group 1, to 41.2 ± 10.1% in group 2, and to 43.2 ± 20.0% in group 3. However, there were no statistically significant differences among the groups ($P = 0.92$ by one-way ANOVA). The CMAP amplitude recovered to 64.6 ± 18.0% after 1 week, and to 85.0 ± 22.7% after 2 weeks in group 1, which was a statistically significant recovery compared to groups 2 and 3 ($P < 0.01$). The amplitude recovered to 52.5 ± 10.6% after 1 week and to 63.1 ± 13.4% after 2 weeks in group 2, and to 50.8 ± 18.1% after 1 week and to 55.9 ± 16.3% after 2 weeks in group 3.

The CMAP latency showed no statistically significant differences among either of the groups or at different times. The latencies on weeks 0, 1, and 2 for each of the groups are provided in Table 1 and compared in Figure 1.

Semiquantitative analysis performed by a neuropathologist using light microscopy (×400) showed that the percentages of degenerated myelin fibers among the total myelin fibers were 2.5 ± 2.1% for group 1, 4.4 ± 1.4% for group 2, and 11.1 ± 6.5% for group 3, and these differences were not statistically significant ($P = 0.17$, Kruskal-Wallis test).

Light microscopic observations of the tissue around the carpal tunnel revealed chronic inflammation and fibrosis. However, there were no significant differences among the groups in terms of the degree of inflammation and fibrosis.

DISCUSSION

Acute Animal CTS Model. The carpal tunnel is an anatomically open structure, but can function as a closed compartment when the pressure increases

due to edema of the surrounding tissues.^{2,3} The electrophysiological findings of acute CTS differ from those observed in idiopathic chronic CTS. Conduction block is the most prominent finding in acute CTS, whereas a delay in the latency is the main electrophysiological finding in idiopathic chronic CTS. The conduction block may result from acute compression of the nerve.^{3,5,8,14,15,31} The animal model used in this study showed conduction block rather than a delay of latency, which is comparable to clinical cases of acute CTS.

When they measured intracarpal pressure using a catheter, Szabo and Chidgey³⁵ reported that the pressure was increased in the acute or subacute cases but not in the chronic cases. This increase in pressure was more vigorous after 10 min of exercise, and took a longer time to return to the preexercise level in those with acute CTS than in normal subjects.³⁵ This suggests a close relationship between the development of acute CTS and the increase in intracarpal pressure. However, many studies have shown that ischemia is related to the development of acute CTS. Seiler et al.³⁰ reported that blood flow to the carpal tunnel, measured by Doppler, normalized after release of the transverse carpal ligament. This suggests that the improvement in symptoms and conduction velocity after release of the ligament results from an improvement of reversible ischemia.¹² The development of acute CTS in patients with ischemic skin lesions, Raynaud's phenomenon, arteriovenous fistula, intraarterial catheterization, and diabetic mononeuropathy also provides supportive evidence that ischemia causes acute CTS.^{2,9,25,27,36,37}

Rydevik et al.²⁶ applied pressure to the tibial nerve of rabbits in vivo under light microscopic observation. Blood flow to the venule was blocked at 20–30 mmHg, the arteriole and intrafascicular capil-

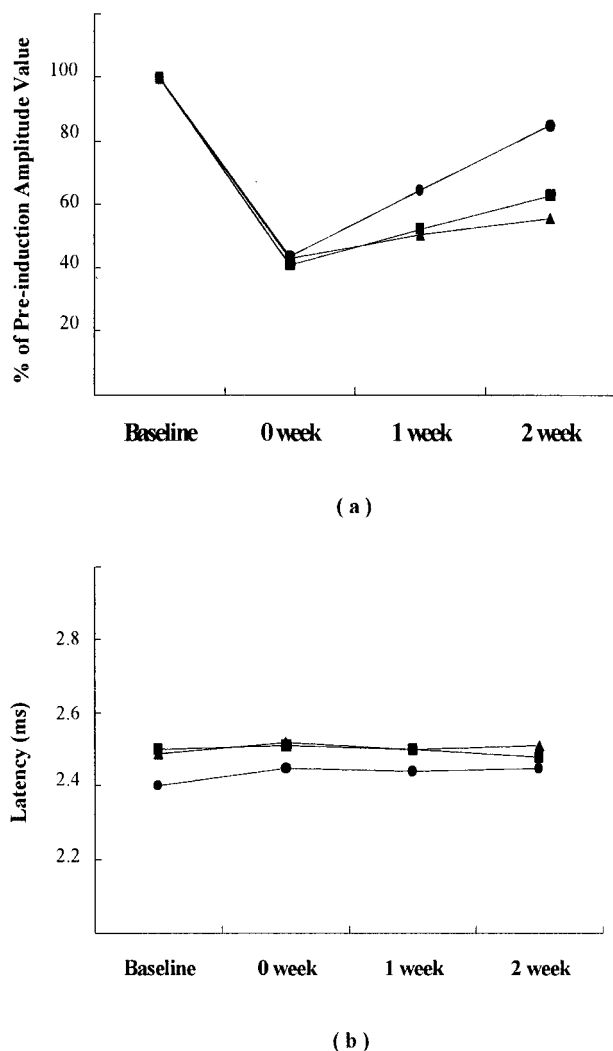


FIGURE 1. Effect of ultrasound therapy on median nerve CMAP at three different power levels. **(a)** Comparison of CMAP amplitude between groups. Improvement was significantly more pronounced in group 1 (1.5 W/cm², filled circles) than in group 2 (0.2 W/cm², filled squares) or group 3 (0.0 W/cm², filled triangles) ($P < 0.05$). **(b)** Comparison of latency between groups. No significant differences due to the ultrasound treatment were observed in any group ($P > 0.05$).

lary was blocked at 40–50 mmHg, and all the blood flow to the nerve was blocked at 60–80 mmHg. In a nerve subjected to a pressure of 400 mmHg for 2 h, blood flow did not recover even after 3 or 7 days.²⁶

Therefore, it is speculated that acute CTS is generated because the increased pressure in the carpal tunnel hinders venous return from the nerve funiculi, leading to edema or ischemia within the funiculi.³³ The electrophysiological changes observed in this study were the same as those observed during ischemia. The degree of the conduction block was proportional to the pressure–time integrals in our pilot study. The animal experimental model used in

this study thus appears to be a suitable model of acute CTS arising from ischemia caused by a sharp increase in the intracarpal pressure.

Histologically, Wallerian degeneration was observed rather than demyelination in some of the large myelinated nerve fibers. However, most fibers were intact, which accords with the electrophysiological findings of conduction block caused by ischemia.^{13,18}

Ultrasound Effect on Acute CTS. Ultrasound is used to treat musculoskeletal disorders such as tendinitis, bursitis, arthritis, or fracture. It is believed that ultrasound increases blood flow, clears the pain mediator, and changes the permeability of the biologic membrane, nerve conduction, and pain threshold.^{6,10,20,38} Therapeutic ultrasound uses frequencies ranging from 0.8–3.0 MHz.²⁰ The results of two clinical trials, in which ultrasound was applied to patients with CTS as a conservative treatment method, have recently been reported. However, the effect of ultrasound treatment for CTS and the manner in which it may work are controversial.

Ebenbichler et al.¹¹ reported that symptoms and electrophysiological parameters were improved when a dose of 1.0 W/cm² ultrasound was applied to patients with CTS over a period of 6 weeks. They suggested that benefit occurred through an antiinflammatory and tissue stimulatory effect of the ultrasound.^{1,4} By contrast, Oztas et al.²⁴ found no significant differences in symptoms or electrophysiological parameters between control and treatment groups, when 1.5 or 0.8 W/cm² of ultrasound was applied over a period of 2 weeks (for 5 min, 5 days per week). They suggested that ultrasound selectively heats the peripheral nerves, which leads to a temporal conduction block of the median nerve. This implies that ultrasound treatment is actually harmful to patients with CTS.³⁹ Sucher³² criticized the treatment method of Oztas et al.,²⁴ however, and suggested that ultrasound be applied to the vicinity of the carpal tunnel rather than to the median nerve directly, in order to reduce tissue inflammation around the carpal tunnel.

A study on the effect of ultrasound therapy for the acute form of CTS has not been reported, to our knowledge. Hong et al.¹⁷ investigated the effect of ultrasound therapy in rats with experimental compression neuropathy. They reported that nerve recovery was facilitated by a nonthermal ultrasound dose, whereas a thermal dose of ultrasound had the opposite effect. They suggested that nerve recovery might be enhanced by an increase in blood flow caused by the application of nonthermal ultrasound

doses, but that thermal ultrasound doses would hinder nerve recovery because of overheating and mechanical damage.

In our study, CMAP was notably improved when a thermal ultrasound dose was used. This suggests that the recovery of conduction block in the median nerve was facilitated by an increased blood flow, which is analogous to the thermal effect of ultrasound. By contrast, the effect of a nonthermal dose was only equivalent to the effect in the placebo group. We found no differences in the degree of inflammation and edema of the peripheral tissues between the three groups. Therefore, we believe that ultrasound treatment works directly on the nerve itself and by the thermal effect, which induces an increase in blood flow.

Previous studies, which reported that the release of the transverse carpal ligament resulted in an increase in blood flow and an improvement in symptoms and electrophysiological data, also suggest that ultrasound works by increasing blood flow in thermal doses.^{12,28,29} However, it is still uncertain whether ultrasound works directly on the nerve or affects the nerve secondarily by resolving the edema and inflammation of surrounding tissue.^{1,4,17,32,39} Further studies to determine to what extent the thermal and nonthermal doses of ultrasound alter tissue structure, vascular dynamics, and temperature in this model may be informative.

This work was presented at the 47th annual meeting of the American Association of Electrodiagnostic Medicine, Philadelphia, Pennsylvania, September 2000. This study was supported by a research grant (04-1999-067-0) from the Clinical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea.

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Ultrasound treatment for treating the carpal tunnel syndrome: randomised “sham” controlled trial

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Abstract

Objective: To assess the efficacy of ultrasound treatment for mild to moderate idiopathic carpal tunnel syndrome.

Design: Randomised, double blind, “sham” controlled trial with assessments at baseline, after 2 weeks’ and 7 weeks’ treatment, and at a follow up assessment 6 months later (8 months after baseline evaluation).

Setting: Outpatient clinic of a university department of physical medicine and rehabilitation in Vienna.

Subjects: 45 patients with mild to moderate bilateral carpal tunnel syndrome as verified by electroneurography.

Intervention: 20 sessions of ultrasound (active) treatment (1 MHz, 1.0 W/cm², pulsed mode 1:4, 15 minutes per session) applied to the area over the carpal tunnel of one wrist, and indistinguishable sham ultrasound treatment applied to the other. The first 10 treatments were performed daily (5 sessions/week); 10 further treatments were twice weekly for 5 weeks.

Main outcome measures: Score of subjective symptom ratings assessed by visual analogue scale; electroneurographic measures (for example, motor distal latency and sensory antidromic nerve conduction velocity).

Results: Improvement was significantly more pronounced in actively treated than in sham treated wrists for both subjective symptoms ($P < 0.001$, paired t test) and electroneurographic variables (motor distal latency $P < 0.001$, paired t test; sensory antidromic nerve conduction velocity $P < 0.001$, paired t test). Effects were sustained at 6 months’ follow up.

Conclusion: Results suggest there are satisfying short to medium term effects due to ultrasound treatment in patients with mild to moderate idiopathic carpal tunnel syndrome. Findings need to be confirmed, and ultrasound treatment will have to be compared with standard conservative and invasive treatment options.

Introduction

The carpal tunnel syndrome, caused by compression of the median nerve at the wrist, is considered the most common entrapment neuropathy.¹ Patients complain of paraesthesia (with or without numbness or pain) involving the fingers innervated by the median nerve, and a weakness of thumb abduction. Symptoms are

worst at night and often wake the patient. Standard treatments include splints, local injection of corticosteroids, and surgical decompression. Benefit from non-surgical treatment, however, seems to be limited,² and not all patients respond to surgery.³⁻⁴

Ultrasound treatment within an intensity range of 0.5-2.0 W/cm² may have the potential to induce various biophysical effects within tissue.⁵⁻⁶ Experiments on the stimulation of nerve regeneration⁷ and on nerve conduction by ultrasound treatment⁸⁻⁹ and findings of an anti-inflammatory effect of such treatment¹⁰ support the concept that ultrasound treatment might facilitate recovery from nerve compression.⁷ However, few studies report a benefit of ultrasound treatment in the carpal tunnel syndrome under clinical conditions.¹¹⁻¹² We sought to investigate the clinical efficacy of pulsed ultrasound in the treatment of idiopathic carpal tunnel syndrome by means of a rigorous, controlled clinical trial.

Material and methods

Patients

Over two years patients with clinically suspected carpal tunnel syndrome referred to the outpatient clinic of the department of physical medicine and rehabilitation of the University of Vienna were invited to take part in this randomised, double blind study of ultrasound treatment versus “sham” ultrasound treatment (fig 1).

We diagnosed the carpal tunnel syndrome by using standard electrophysiological criteria.¹³⁻¹⁴ Criteria for inclusion in the study were bilateral, idiopathic carpal tunnel syndrome; mild to moderate pain lasting more than three months; and written informed consent. Patients were excluded if they had secondary entrapment neuropathies, systemic diseases with increased risk of the carpal tunnel syndrome, or electroneurographic and clinical signs for axonal degeneration of the median nerve; had gained surgical relief of the syndrome; had been treated with ultrasound for the syndrome; had a history of steroid injections into the carpal tunnel; or had required regular analgesic or anti-inflammatory drugs.

Intervention

Ultrasound treatment was administered as monotherapy for 15 minutes per session to the area over the

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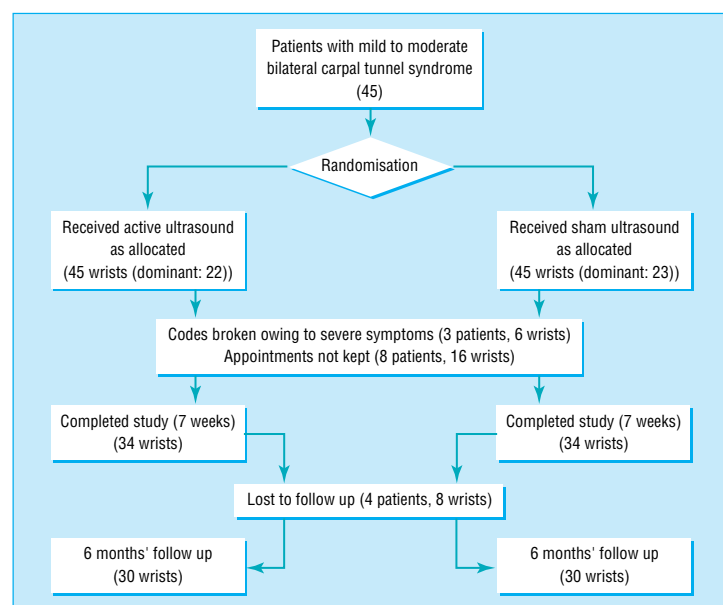


Fig 1 Trial profile

carpal tunnel at a frequency of 1 MHz and an intensity of 1.0 W/cm², pulsed mode 1:4, with a transducer of 5 cm² (Sonodyn, Siemens) and with aquasonic gel as couplant. The machine was standardised initially, and the output was controlled regularly on a simple underwater radiation balance. An on/off key introduced into the transducer circuit allowed mock insonation to be given to a sham group without affecting the normal ultrasonic output when the key was turned to the "on" position. The first 10 treatments of a total of 20 ultrasound treatments were performed daily 5 times a week for 2 weeks, and the second 10 treatments twice a week for another 5 weeks.

For occasional pain relief, analgesics (usually tramadol) were allowed, but not non-steroidal or steroidal antirheumatics.

Outcome measures

Primary

Primary outcome measures for each wrist comprised (a) a sum score of subjective symptoms consisting of ratings of main complaints and sensory loss and (b) quantification of electroneurographic measurements. Main complaints were defined as complaints related to pain or paraesthesia, or to both, which the patient considered the most important ones at baseline. Severity of complaints at the clinical examination, and the worst complaints experienced within 3 days before the consultation were quantified by the study physician (GRE) by means of a coloured visual analogue scale, on which the patients could indicate their assessment along a distance of 10 cm, ranging from white ("no complaints at all") to red ("the most intense complaints I can imagine"). Sensory loss (hypalgesia or hyperpathia, or both) was assessed by means of a sharp pin wheel and compared with "normal" sensation in the fifth digit. Quantification was again by coloured visual analogue scale ("no difference at all" to "greatest possible difference").

All electroneurographic measurements were performed with a Viking II Nicolet (EMS, Madison, USA)

electromyography device. Briefly, median motor nerve conduction was measured at the wrist and elbow with bipolar surface disc electrodes. Median distal motor latency was recorded with cathodes 6.5 cm apart. Antidromic sensory nerve action potentials were recorded from the wrist to the second digit, with ring electrodes placed around the proximal and distal interphalangeal joints. At least 15 sensory nerve action potentials were averaged, and antidromic sensory nerve conduction velocity was calculated as appropriate. The skin temperature of the forearm was kept constant at 32–33°C during all treatments.¹⁵

Secondary

Secondary outcome measures comprised (a) quantification of physical functioning and (b) the patients' general improvement. Tests of physical functioning comprised dynamometric measurements (dynamometer by Preston, New York) of hand grip and finger pinch strength. The patients' positioning was standardised, and the average force of three consecutive trials was calculated. The patients rated their overall change at the end of the treatment series on a five point ordinal scale (1 = free of symptoms, 5 = much worse).

Other factors

At each appointment the patients rated their main complaint without being reminded of the ratings they had made at previous appointments. Drugs taken for pain relief were registered and side effects of the ultrasound treatment reported.

Electrophysiological measurements and clinical examinations were performed before the first treatment session, after 10 sessions (week 2), and after the last session (week 7). A follow up was performed six months later (8 months after baseline evaluation). After the follow up examination the treatment code was broken, and patients were either discharged or offered an alternative treatment.

Sample size

A sample size calculation was performed based on the assumptions that the main outcome measurement (changes in sum score between baseline and end of treatment on visual analogue scale) is continuous in nature, fairly normally distributed, and that an additional improvement in the intervention side of 10 percentage points (standard deviation = 15 percentage points) is considered clinically relevant. If the incidence of the carpal tunnel syndrome on one wrist could be considered completely independent from the incidence on the other wrist, 36 independent observations in each group would be necessary to detect that difference at the 5% level ($\alpha = 0.05$) with an 80% chance ($\beta = 0.2$). Synchronicity of the carpal tunnel syndrome in both wrists happens in about one third of all cases, but to our knowledge no evidence exists that the natural course of symptoms goes strictly in parallel in these cases. In addition, systemic interventions that would probably affect both wrists, such as pain killers, were among the exclusion criteria. Taken together, 45 to 50 independent observations in each group might be a sensible estimate.

Statistics

Longitudinal changes between wrists were compared, with two tailed *t* tests for paired samples for fairly normally distributed variables (visual analogue scores and force measurements) and Wilcoxon tests for skewed data. Subsequently, a χ^2 analysis was performed on dichotomised data of the mean score of subjective symptoms, with an overall improvement of more than 35 percentage points from baseline values as cut off point.

Assignment

A randomisation list was produced with a random number generator of a popular spreadsheet program (Lotus Symphony). After the eligible patients had been enrolled, an ultrasound therapist not involved in the treatment allocated the dominant wrist of each consecutive patient to ultrasound or sham treatment (the patient's other wrist received the other treatment) by means of sequentially numbered sealed opaque envelopes containing the group allocation (active or sham). This therapist was the only person aware of treatment allocation during the trial.

Blinding

The patients, GRE, and the therapists who delivered the ultrasound treatment were all unaware of the treatment allocation. Only the therapist who was in charge of group allocation switched the ultrasonic generator to the respective modes before each treatment session (see above). This procedure allowed blinding of both the patients and the therapists delivering the treatment. Intensity of ultrasound treatment was below sensitivity threshold.

Results

Baseline evaluation

Forty five patients with bilateral carpal tunnel syndrome (90 wrists) fulfilled all inclusion criteria; 11 (24%) of these patients discontinued treatment after randomisation (8 patients early after randomisation because of non-compliance in keeping appointments, and 3 patients because of excessive pain requiring additional therapeutic measures). Thus 34 patients—that is, 34 actively treated and 34 sham treated wrists—completed the study. Their characteristics did not differ from the original 45 patients in the study. Thirty of them (67% of the initial 45 patients) completed a follow up at 6 months.

The wrists were similar in terms of the duration of current episodes of main complaints regardless of randomisation group (table 1). There were slight group imbalances at baseline. Most complaints in the actively treated group were significantly more severe ($P=0.05$, Wilcoxon test) when rated on the visual analogue scale. Baseline differences were also present in the mean score of physical functioning and strength of hand grip, whereas finger pinch was comparable.

Other subjective symptoms—for example, scores of main complaints, sensory loss, and the mean score of all subjective symptoms—were similar at baseline. Electroneurography, motor distal latency, peak to peak amplitude, and antidromic sensory nerve conduction velocity did not differ significantly between wrists.

Table 1 Demographic data and baseline characteristics of patients who completed study, according to which group (active or sham ultrasound) their dominant wrist was randomised to. Values are means (SD) unless stated otherwise

Variable	Treatment	
	Active	Sham
No of subjects who completed the study	34	
Age (years)	51 (15)	
Body mass index (kg/m ²)	25.9 (5.1)	
No of wrists with complaints	29	27
No of wrists with sensory loss	25	19
Duration of current episode of main complaints (months)	7.8 (6.7)	7.2 (6.5)
Subjective symptoms:		
Score of all subjective symptoms	4.1 (2.1)	3.3 (1.5)
Main complaint (cm)*	3.3 (2.8)	2.0 (1.9)
Worst complaint (cm)*	6.5 (2.6)	5.8 (2.8)
Sensory loss (cm)*	2.4 (2.4)	2.0 (2.4)
Physical functioning:		
Score of physical functioning	21.3 (11.9)	25.5 (11.3)
Handgrip strength (kg)	15.8 (10.9)	19.8 (10.0)
Finger pinch ($\times 0.2$ kg)	5.5 (1.8)	5.8 (1.8)
Electroneurography:		
Motor distal latency (ms)	5.2 (1.0)	5.2 (1.2)
Peak to peak amplitude	14.5 (3.4)	14.6 (3.7)
Antidromic sensory nerve conduction velocity wrist-digit II (m/s)	40.0 (7.2)	42.1 (7.2)

*Distance along a coloured visual analogue scale, on which the patients indicated their assessment (white, 0=minimum complaint; red, 10=maximum complaint). See methods section for further details.

Effect of treatment

Subjective symptoms

Table 2 and figure 2 show longitudinal changes of subjective symptoms. Improvement in the mean score of all ratings of subjective symptoms was significantly more pronounced in the actively treated wrists at week 2 ($P<0.008$), at the end of treatment ($P<0.0001$), and at the 6 month follow up ($P<0.0001$).

Satisfactory improvement or complete remission of symptoms was observed in 68% (23/34) of the wrists receiving active treatment versus 38% (13/34) of those receiving sham treatment ($P<0.001$; relative risk reduction 48%) at the end of the treatment series, and in 74% (22/30) versus 20% (6/30) ($P<0.001$; 67%) at 6 months' follow up.

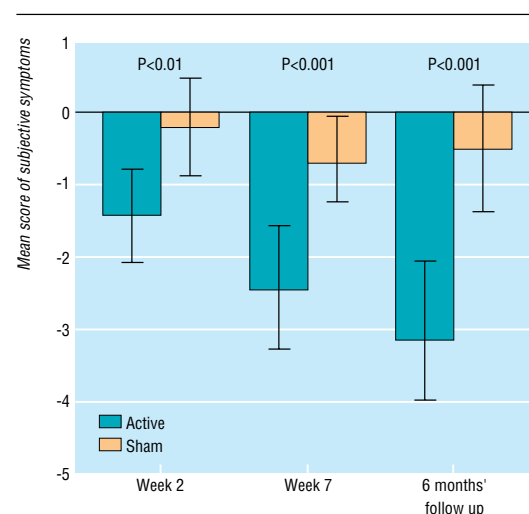


Fig 2 Mean change (and 95% confidence intervals) from baseline score for all subjective symptoms (active versus sham treatment) at week 2, end of treatment, and 6 months' follow up (paired *t* test)

Table 2 Mean change (95% confidence interval) from baseline values for outcome measures at week 2, at end of treatment (week 7), and 6 months later

Outcome measure	Week 2	End of therapy	6 months' follow up
Subjective symptoms			
Mean change in main complaints (cm)*:			
Sham	0.05 (−0.48 to 0.58)	−0.17 (−0.92 to 0.57)	−0.08 (−1.06 to 0.90)
Active	−1.05 (−1.91 to −0.19)	−2.14 (−3.15 to −1.12)	−2.76 (−3.79 to −1.73)
Paired difference (<i>t</i> test)	1.1 (0.23 to 1.98)	1.96 (0.91 to 3.01)	2.26 (1.49 to 3.88)
P value (2 tailed)	0.015	0.001	<0.0005
Mean change in worst complaints (cm)*:			
Sham	−0.90 (−2.24 to 0.43)	−1.56 (−2.58 to −0.54)	−0.95 (−2.43 to 0.54)
Active	−2.20 (−3.16 to −1.25)	−3.91 (−5.07 to −2.75)	−4.78 (−5.85 to −3.70)
Paired difference (<i>t</i> test)	1.30 (−0.38 to 2.98)	2.35 (0.92 to 3.78)	3.83 (2.32 to 5.34)
P value (2 tailed)	0.125	0.002	<0.0005
Mean change in sensory loss (cm)*:			
Sham	0.42 (−0.29 to 1.13)	−0.07 (−0.86 to 0.72)	−0.08 (−0.91 to 0.76)
Active	−0.82 (−1.69 to 0.05)	−1.14 (−1.99 to −0.29)	−1.60 (−2.55 to −0.65)
Paired difference (<i>t</i> test)	1.24 (0.33 to 2.15)	1.07 (0.31 to 1.83)	1.53 (0.85 to 2.20)
P value (2 tailed)	0.009	0.007	<0.0005
Physical functioning			
Mean change in hand grip strength (kg):			
Sham	−0.61 (−1.88 to 0.66)	−0.09 (−2.04 to 1.85)	−1.99 (−4.08 to 0.09)
Active	0.71 (−1.35 to 2.77)	3.87 (2.06 to 5.67)	5.44 (2.91 to 7.96)
Paired difference (<i>t</i> test)	−1.32 (0.35 to −2.99)	−3.96 (−2.01 to −5.90)	−7.43 (−5.22 to −9.64)
P value (2 tailed)	0.118	<0.0005	<0.0005
Mean change in pinch strength (kg):			
Sham	−0.20 (−0.25 to −0.15)	0.06 (−0.26 to 0.38)	−0.22 (−0.38 to −0.06)
Active	−0.01 (−0.13 to 0.12)	0.33 (0.17 to 0.50)	0.49 (0.28 to 0.70)
Paired difference (<i>t</i> test)	−0.19 (0.43 to −0.81)	−0.27 (0.37 to −0.91)	−0.71 (−0.15 to −1.27)
P value (2 tailed)	0.537	0.392	0.014
Electroneurography			
Mean change in motor distal latency (ms):			
Sham	0.04 (−0.08 to 0.15)	0.06 (−0.08 to 0.21)	0.04 (−0.10 to 0.19)
Active	−0.23 (−0.37 to −0.10)	−0.55 (−0.71 to −0.39)	−0.31 (−0.45 to −0.18)
Paired difference (<i>t</i> test)	0.27 (0.11 to 0.42)	0.61 (0.43 to 0.79)	0.36 (0.18 to 0.54)
P value (2 tailed)	0.001	<0.0005	<0.0005
Mean change in antidromic sensory nerve conduction velocity (m/s):			
Sham	−0.84 (−1.07 to −0.62)	−0.89 (−1.11 to −0.66)	−0.27 (−0.51 to −0.03)
Active	4.50 (4.34 to 4.66)	7.35 (6.98 to 7.71)	2.69 (2.39 to 2.99)
Paired difference (<i>t</i> test)	−5.34 (−3.58 to −7.11)	−8.23 (−6.22 to −10.24)	−2.96 (−1.66 to −4.66)
P value (2 tailed)	<0.0005	p<0.0005	0.001

*Distance along a coloured visual analogue scale, on which the patients indicated their assessment (white, 0=minimum complaint; red, 10=maximum complaint). See methods section for further details.

Electroneurography

The results of electroneurography are shown in table 2. Motor distal latency decreased with active treatment and remained unchanged with sham treatment both at the end of treatment and at 6 months' follow up (end of treatment: active −0.55 ms (95% confidence interval −0.71 to −0.39) and sham 0.06 ms (−0.08 to 0.21); at follow up: −0.31 ms (−0.45 to −0.18) and 0.04 ms (−0.10 to 0.19); $P < 0.001$ for both time periods).

Similar significant changes in the velocity of sensory nerve conduction were observed at the end of treatment and at 6 months' follow up with active treatment, whereas velocity remained unchanged with sham treatment ($P < 0.0001$ between groups).

Physical functioning

Hand grip and finger pinch strength had improved significantly with active treatment at the end of treatment and at 6 months' follow up (table 2).

Other measurements

Patients' ratings of overall improvement at the end of treatment significantly favoured active over sham treatment (Mann-Whitney U test $P = 0.002$). Good or excel-

lent treatment results were stated by 76% (26/34) of the patients for actively treated wrists versus 32% (11/34) for sham treated wrists.

At 6 months' follow up 28 patients showed an unsatisfactory outcome (9 actively treated and 19 sham treated wrists) and were offered further treatment. Subsequently 13 patients were offered ultrasound treatment and splints for their sham treated wrists, and 10 wrists (3 sham treated) were injected with steroids. Surgical relief of the carpal tunnel syndrome was planned for 5 patients (3 sham treated wrists).

Average consumption of analgesics during treatment and follow up phase was low: 8 out of the 34 patients occasionally took analgesics, and three patients were off work. No side effects due to ultrasound treatment were reported.

Discussion

An increase in pressure in the carpal tunnel is usually caused by non-specific flexor tenosynovitis.¹⁶ Chronic focal compression of a nerve trunk can cause focal demyelination by mechanical stress deforming the myelin lamellae. Ischaemia also plays a pathogenic role

Key messages

- Chronic entrapment of the median nerve at the wrist (the carpal tunnel syndrome) is probably the most common peripheral nerve lesion
- No satisfactory conservative treatment is available at present
- Twenty sessions of ultrasound treatment show good short and medium term efficacy in patients with bilateral, mild to moderate forms of the carpal tunnel syndrome
- Optimal treatment schedules of ultrasound treatment alone or in combination with other non-surgical treatments await elucidation

in the carpal tunnel syndrome. It could account for intermittent paraesthesia that occurs at night or with wrist flexion.² The carpal tunnel syndrome is often observed bilaterally. Symptoms are usually markedly worse on one (mostly the dominant) side.

Conservative treatment approaches seem to offer clear advantages over surgical treatment of the carpal tunnel syndrome. Recent studies have confirmed short term effects of steroid injections into the carpal tunnel, with modest or complete pain relief in up to 92% of the patients, although long term recurrence rates seem variable.¹⁷⁻¹⁹ Potential adverse effects to nerves and tendons with repeated injections have limited the value of this treatment.²⁰⁻²¹ Palmar wrist splints worn at night seem suitable only when symptoms are mainly nocturnal,²² and ergonomic strategies have not yet been evaluated.

The findings of the present study confirm preliminary data that ultrasound treatment may facilitate recovery from the carpal tunnel syndrome.¹¹⁻¹² Given the favourable response rate of 68% of patients at the end of treatment, ultrasound treatment may be similar in effectiveness to steroid injections or wrist splinting; improvements persisting for at least 6 months in most patients might even suggest the potential superiority of ultrasound treatment.

Serial ratings by patients of overall improvement suggest that ultrasound treatment would be best administered every day. Frequent treatment, however, is time consuming (as seen by the relatively high drop out rate in our study), but ultrasound treatment could be performed by compliant patients at home.

According to the pathophysiology of the carpal tunnel syndrome, ultrasonography might elicit anti-inflammatory and tissue stimulating effects, as already shown experimentally²³ and in recent clinical trials.¹⁰⁻²⁴

Conclusion

Our trial suggests that ultrasound treatment has good short term effectiveness and even yields satisfying medium term effects in patients with mild to moderate idiopathic carpal tunnel syndrome. Further research is required to confirm independently these findings, to evaluate optimal treatment schedules with this method, and to investigate whether ultrasound treatment or one of the non-surgical treatments alone or in combination is superior, or whether early decom-

pression may provide better long term results with fewer eventual neurological deficits.

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Contributors: GRE initiated the study, coordinated the formulation of the primary research hypothesis, designed the study, participated in data collection and data analysis, interpreted the findings, and wrote the paper. KLR participated in the design, carried out the data analysis and interpretation, and wrote the paper. PN, GFW, FU, and A-HG participated in the design, data collection, and the interpretation of results and helped to write the paper. VF participated in the design and the interpretation of results and helped to write the paper. GRE and KLR are guarantors for the paper.

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Variations in population health status: results from a United Kingdom national questionnaire survey

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Abstract

Objective: To measure the health of a representative sample of the population of the United Kingdom by using the EuroQoL EQ-5D questionnaire.

Design: Stratified random sample representative of the general population aged 18 and over and living in the community.

Setting: United Kingdom.

Subjects: 3395 people resident in the United Kingdom.

Main outcome measures: Average values for mobility, self care, usual activities, pain or discomfort, and anxiety or depression.

Results: One in three respondents reported problems with pain or discomfort. There were differences in the perception of health according to the respondent's age, social class, education, housing tenure, economic position, and smoking behaviour.

Conclusions: The EQ-5D questionnaire is a practical way of measuring the health of a population and of detecting differences in subgroups of the population.

Introduction

The measurement of health is central to the evaluation of health care. By observing the extent of changes in health the benefits and disbenefits of health care for both patients and groups of patients can be evaluated; over the past 25 years several generic measures of health have been developed for use in this way.¹⁻⁸ These instruments were designed for use as general purpose measures of health, independent of diagnostic categorisation or disease severity. Information based on such measures is useful for establishing the degrees of morbidity in the community, enabling different population subgroups to be compared, which would help in assessing health needs or in informing those responsible for allocating health resources. Periodic reassessment of health could provide important data on the extent of any changes in the health of a population—for example, the extent to which the population is achieving national targets for health. If such standardised information was also routinely collected on individual patients it would provide a simple means of evaluating the outcomes of their health care.

We report on a study in which the EuroQoL EQ-5D questionnaire⁹ was fielded in a survey of the population of the United Kingdom, conducted as part of a wider study of practical ways of measuring health related quality of life.¹⁰

Subjects and methods

EQ-5D questionnaire

The EQ-5D questionnaire is a generic measure of health status developed by the EuroQoL Group, an international research network established in 1987 by researchers from Finland, the Netherlands, Sweden,

and the United Kingdom. The EQ-5D questionnaire defines health in terms of five dimensions: mobility, self care, usual activities (work, study, housework, family, or leisure), pain or discomfort, and anxiety or depression. Each dimension is subdivided into three categories, which indicate whether the respondent has no problem, a moderate problem, or an extreme problem (appendix). Combinations of these categories define a total of 243 health states. The EQ-5D questionnaire comprises two pages; on the first page respondents record the extent of their problem in each of the five dimensions and on the second page they record their perception of their overall health on a visual analogue scale (0 denoting the worst imaginable health state and 100 denoting the best imaginable health state). The validity and reliability of the EQ-5D questionnaire have been tested,¹¹⁻¹³ as has its application in a range of patient groups.¹⁴⁻¹⁶ Since the original survey reported here, the EQ-5D questionnaire has been fielded in three national surveys, including the English national health survey—an interview-based survey of about 16 000 people. The EQ-5D questionnaire has also been used in population surveys in Spain, Germany, and Canada.

Survey design and methods

Members of the public aged 18 and over were interviewed as part of a national survey. No upper age limit was stipulated. The sample was based on addresses in England, Scotland, and Wales, selected by postcode.¹⁷ Eighty postcode areas were chosen, proportionately to the number of addresses in each area, after these areas had been stratified by regional health authority, socioeconomic group, and population density. Seventy six addresses were selected from each postcode area, yielding a total of 6080 addresses. At each of these addresses one adult aged 18 or over was selected using a Kish grid.¹⁸ Individuals in institutions, hostels, care homes, or bed and breakfast accommodation were excluded from the sample. Of the selected addresses, 12% were unproductive as they were non-residential, empty, or untraceable. The final sample comprising 3395 subjects was representative of the general population with respect to age, sex, and social class. During the interview, respondents completed the EQ-5D questionnaire and provided information on age, sex, marital state, education, employment, housing tenure, and smoking behaviour. The interviews took place during the last quarter of 1993.

Analysis mainly compared the differences between the population subgroups. It was hypothesised that more health problems would be reported with increasing age, with lower social class, for those registered sick or disabled, and for smokers. χ^2 Tests were used for the analysis of the descriptive profile data, and Student's *t* test was used to test for subgroup differences in the visual analogue scale data.

Results

A moderate problem on at least one dimension was reported by 42% of respondents, whereas only 6% of respondents reported any extreme problem (table 1). Problems were most often recorded in the pain or discomfort dimension. In subsequent analyses, moderate and extreme categories of each dimension were combined.

The mean state of health recorded on the visual analogue scale was 82.5 (SD 17).

Health and age

The rates of reported problems increased significantly with age ($P < 0.001$) for all dimensions (table 2); an exception to this general pattern was the anxiety/depression dimension, which peaked at 28% of respondents aged 60 to 69 and then decreased slightly.

Figure 1 shows the mean visual analogue scale values for each age group and the 95% confidence interval. The mean value decreased from about 87 in the youngest age group to 72 in the oldest age group. Mean values did not differ significantly in the 20 to 49 age range but decreased significantly for respondents aged ≥ 50 ($P < 0.001$).

Health and sex

Women aged ≥ 70 tended to report higher rates of problems than did men of the same age (table 2). A systematic difference in rates was found across all age groups on the anxiety/depression dimension, with women reporting significantly higher rates than men ($P < 0.05$). No significant differences were found in the visual analogue scale scores for men and women.

Health and marital status

Respondents who were widowed, separated, or divorced reported significantly more problems on all five dimensions ($P < 0.001$). Scores on the visual analogue scale for this group were also significantly lower than for respondents living alone or for those

Table 1 Numbers (percentages) of respondents reporting a problem in each EuroQoL dimension

EuroQoL dimension	Problem		
	Moderate	Extreme	Any
Mobility	620 (18.3)	3 (0.1)	623 (18.4)
Self care	139 (4.1)	5 (0.1)	144 (4.2)
Usual activities	481 (14.2)	70 (2.1)	551 (16.3)
Pain/discomfort	988 (29.2)	129 (3.8)	1117 (33.0)
Anxiety/depression	648 (19.1)	62 (1.8)	710 (20.9)
Any dimensions*	1441 (42.4)	212 (6.2)	1456 (43.1)

*Although row totals within dimension are internally consistent, there is apparent anomaly in the final row. 1441 respondents reported a moderate problem in at least one dimension and 212 reported an extreme problem; these two dimensions are not mutually exclusive as respondents may have reported an extreme problem in one dimension, with no intermediate level of problem being reported for remaining dimension. Hence total of 1456 does not equate to addition of two previous table entries.

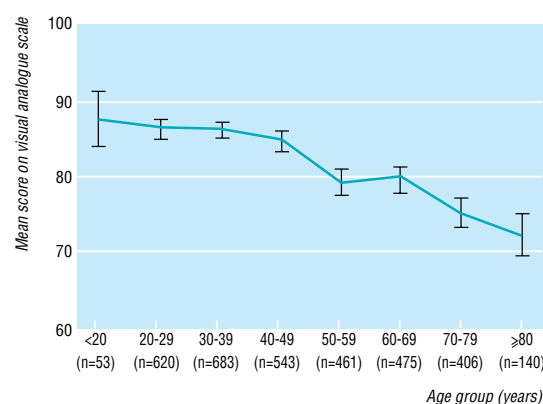


Fig 1 Mean self rated health status of respondents

with a partner (means 77, 84, and 84 respectively, $P < 0.001$).

Health and social class

After the effects of age were controlled for, there were significant differences in the rates of reported problems when respondents were grouped according to social class (table 3).

Table 2 Numbers (percentages) of respondents reporting any problem, by age group and sex

EuroQoL dimension	Age group (years)						
	20-29	30-39	40-49	50-59	60-69	70-79	≥ 80
Mobility							
All respondents	31 (5.0)	53 (7.8)	56 (10.3)	101 (21.9)	140 (29.3)	162 (39.8)	80 (56.7)
Men	15 (5.7)	24 (8.0)	23 (9.3)	53 (25.9)	73 (34.6)	57 (33.5)	21 (45.7)
Women	16 (4.5)	29 (7.6)	33 (11.1)	48 (18.7)	67 (25.1)	105 (44.3)	59 (62.1)
Self care							
All respondents	6 (1.0)	11 (1.6)	23 (4.2)	24 (5.2)	27 (5.7)	30 (7.4)	23 (16.3)
Men	3 (1.1)	6 (2.0)	10 (4.0)	13 (6.3)	15 (7.1)	13 (7.6)	5 (10.9)
Women	3 (0.8)	5 (1.3)	13 (4.4)	11 (4.3)	12 (4.5)	17 (7.2)	18 (18.9)
Usual activity							
All respondents	44 (7.1)	59 (8.6)	59 (10.8)	101 (21.9)	118 (24.7)	107 (26.3)	62 (44.0)
Men	23 (8.7)	22 (7.3)	23 (9.3)	51 (25.0)	61 (28.9)	42 (24.7)	19 (41.3)
Women	21 (5.9)	37 (9.7)	36 (12.1)	50 (19.4)	57 (21.4)	65 (27.4)	43 (45.3)
Pain/discomfort							
All respondents	98 (15.8)	132 (19.3)	141 (25.9)	202 (43.7)	221 (46.2)	228 (56.0)	85 (60.3)
Men	39 (14.8)	56 (18.7)	59 (24.0)	85 (41.5)	105 (49.8)	86 (50.6)	25 (54.3)
Women	59 (16.6)	76 (19.8)	82 (27.5)	117 (45.5)	116 (43.4)	142 (59.9)	60 (63.2)
Anxiety/depression							
All respondents	83 (13.4)	119 (17.4)	102 (18.7)	126 (27.2)	134 (28.0)	103 (25.3)	35 (24.8)
Men	27 (10.2)	46 (15.3)	39 (15.8)	53 (25.9)	54 (25.6)	29 (17.1)	8 (17.4)
Women	56 (15.8)	73 (19.1)	63 (21.1)	73 (28.3)	80 (30.0)	74 (31.2)	27 (28.4)

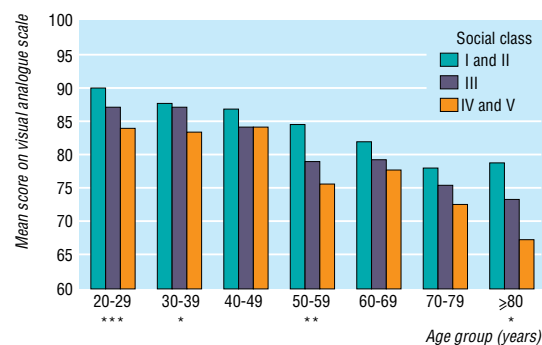
Table 3 Numbers (percentages) of respondents reporting any problem, by age group and social class (based on respondent's own current or most recent occupation as classified by registrar general)

EuroQoL dimension	Age group (years)						
	20-29	30-39	40-49	50-59	60-69	70-79	≥80
Mobility							
Social class:							
I and II	6 (3.6)	18 (7.6)	15 (7.6)	17 (14.3)	42 (28.4)	24 (29.6)	11 (47.8)
III	12 (4.4)	21 (7.3)	26 (11.8)	47 (23.5)	56 (26.7)	80 (39.8)	36 (57.1)
IV and V	11 (7.7)	9 (6.3)	15 (12.4)	36 (26.5)	40 (36.7)	52 (46.4)	28 (59.6)
Self care							
Social class:							
I and II	1 (0.6)	4 (1.7)	7 (3.5)	5 (4.2)	7 (4.8)	3 (3.7)	3 (13.0)
III	2 (0.7)	4 (1.4)	10 (4.5)	10 (5.0)	12 (5.7)	17 (8.5)	7 (11.8)
IV and V	2 (1.4)	2 (1.4)	6 (5.0)	9 (6.7)	7 (6.4)	10 (8.9)	11 (23.4)
Usual activities							
Social class:							
I and II	11 (6.5)	16 (6.8)	19 (9.6)	17 (14.3)	37 (25.0)	19 (23.5)	8 (34.8)
III	16 (5.9)	20 (7.0)	23 (10.4)	45 (22.5)	46 (21.9)	54 (26.9)	28 (44.4)
IV and V	13 (9.1)	18 (12.6)	16 (13.2)	38 (27.9)	32 (29.6)	32 (28.6)	21 (44.7)
Pain/discomfort							
Social class:							
I and II	24 (14.3)	39 (16.5)	38 (19.2)	33 (27.7)	62 (41.9)	36 (44.4)	9 (39.1)
III	42 (15.6)	45 (15.7)	69 (31.4)	98 (49.0)	93 (44.3)	111 (55.2)	43 (68.3)
IV and V	26 (18.2)	41 (28.7)	33 (27.3)	69 (50.7)	62 (56.9)	77 (68.8)	29 (61.7)
Anxiety/depression							
Social class:							
I and II	15 (8.9)	37 (15.6)	31 (15.7)	25 (21.0)	28 (18.9)	14 (17.3)	6 (26.1)
III	36 (13.3)	47 (16.4)	41 (18.6)	59 (29.4)	58 (27.6)	55 (27.4)	13 (20.6)
IV and V	25 (17.5)	33 (23.1)	29 (24.0)	39 (28.7)	45 (41.3)	31 (27.7)	14 (29.8)

Rates of reported problems from respondents in social classes III and IV were between 20% and 120% higher than rates in respondents from social classes I and II; the largest differences were for the pain/discomfort ($P < 0.01$) and anxiety/depression ($P < 0.01$) dimensions. Rates did not differ significantly for the mobility and self care dimensions. Figure 2 shows that respondents from social classes I and II had consistently higher levels of reported health as measured by the visual analogue scale than respondents from the two other social classes. Respondents from social classes I and II had a 5 point advantage on the visual analogue scale over respondents from social classes IV and V of the same age group. The difference was significant for all age groups except for respondents aged 40 to 49 years. The mean scores on the visual analogue scale for respondents from social classes I and II remained above the level of the youngest respondents from social classes IV and V until the 50 to 59 age group.

Health and education

When respondents were classified by education rather than by social class, a similar pattern of differences emerged. Respondents who had received higher or further education reported significantly lower rates of problems with mobility ($P < 0.05$), usual activities ($P < 0.05$), pain/discomfort ($P < 0.01$), and anxiety/depression ($P < 0.01$) than did those who had received no education after leaving school. A similar pattern was seen on the visual analogue scale, with significantly higher scores reported for those who had received higher or further education ($P < 0.001$).

**Fig 2** Effect of social class on self rated health status. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Health and economic status

Significantly higher rates of problems were reported by respondents who were unemployed, sick or disabled, or retired, compared with those in employment or full time education ($P < 0.001$) (table 4). Rates of reported problems for unemployed people were almost twice those of respondents in a salaried job.

When respondents were grouped according to housing tenure, significantly higher rates of problems were recorded on all the dimensions for those living in rented property compared with owner occupiers.

The mean scores on the visual analogue scale of people in work or of people who were studying was significantly higher than for people who were unemployed (87.5 and 82.0 respectively, $P < 0.001$). Similarly, the scores of owner occupiers were significantly higher than for people who rented their accommodation (85.1 and 77.2 respectively, $P < 0.001$).

Table 4 Numbers (percentages) of respondents reporting problems, by employment

Employment	No of respondents	EuroQoL dimension				
		Mobility	Self care	Usual activities	Pain/discomfort	Anxiety/depression
Studying	92	5 (5.4)	1 (1.1)	8 (8.7)	20 (21.7)	15 (16.3)
Salaried job	1636	106 (6.5)	11 (0.7)	109 (6.7)	337 (20.6)	223 (13.6)
Unemployed	196	24 (12.2)	5 (2.6)	21 (10.7)	53 (27.0)	52 (26.5)
Sick or disabled	128	101 (78.9)	48 (37.5)	110 (85.3)	112 (86.8)	79 (61.2)
Retired	761	280 (36.8)	53 (7.0)	211 (27.7)	393 (51.6)	186 (24.4)
Looking after home	524	93 (17.7)	23 (4.4)	79 (15.1)	179 (34.2)	138 (26.3)

*The table excludes 45 respondents whose employment was classed as other and 12 respondents whose details were missing.

Health and smoking behaviour

Respondents who smoked reported significantly higher rates of problems than non-smokers on all dimensions. Non-smokers also recorded significantly higher scores on the visual analogue scale than respondents who smoked (83.4 and 80.4 respectively, $P < 0.001$).

Analysis of variance

Analysis of variance was used to investigate the collective influence of background variables. With the score on the visual analogue scale as the dependent variable and age as a covariate, a main effects model indicated a significant contribution for education ($P < 0.01$), employment ($P < 0.001$), and smoking behaviour ($P < 0.001$). Housing tenure, marital status, and social class were not significant variables in this model.

Disability rates from other national surveys

Respondents who reported any problem in any dimension could be distinguished from respondents who reported no problems whatsoever. This dichotomy can be used to form an arbitrary definition of disability, enabling data to be compared with the findings of other surveys. The general household survey incorporates questions on longstanding illness and recent interference with usual activities.¹⁹ The responses to these questions are combined to give rates of limiting longstanding illness which are published annually. The disability survey by the Office of Population Censuses and Surveys conducted in 1985 included a questionnaire comprising 10 categories: locomotion, reaching and stretching, dexterity, seeing, hearing, personal care, continence, communication, behaviour, and intellectual functioning.²⁰ The rates of disability in people grouped into five year age groups were reported in this survey.²⁰ These data were plotted against disability rates determined from our survey (fig 3). Disability rates based on responses to the EQ-5D questionnaire were 20% to 25% higher than rates from the general household survey for all age groups and about 30% to 40% higher than the 1985 disability survey, until the age of 80.

Discussion

This survey provides an important insight into the health status of the population of the United Kingdom at any one time. Although extreme problems with mobility and self care were rarely reported in this survey, there was a high level of reported problems with pain or discomfort. Over 50% of respondents aged ≥ 70 and about 20% of the youngest respondents reported some problem in this dimension. This finding

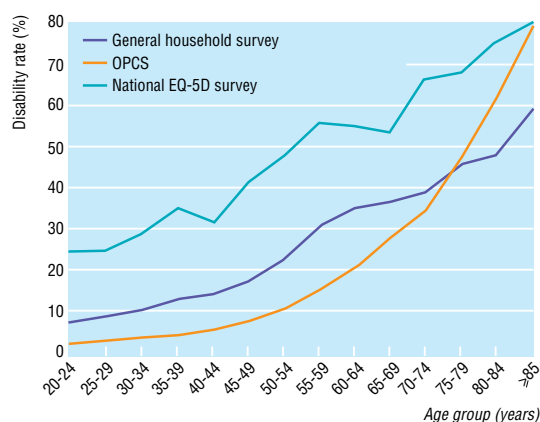


Fig 3 Disability rates from three national surveys

has important implications. Pain does not seem to be a dimension of interest in a national disability survey despite being widely experienced in the community. The omission of a pain category means that it is assigned a zero weight, despite good evidence that it has a powerful influence on society's valuations of states of health.²¹ These factors combine to disadvantage a significant proportion of the general population.

Significant differences were found between population subgroups with respect to age, social class, marital status, employment, education, and smoking behaviour. These findings compare with findings reported elsewhere.²²⁻²⁴ Disability rates based on the EuroQoL classification reflected similar trends to those seen in the general household survey and surveys of the Office of Population Censuses and Surveys, although rates in these surveys were somewhat lower as they were based on a narrower definition of disability.

Population averages

The representativeness of the survey suggests that the results are indicative of the average health status in the general population of the United Kingdom, although it should be borne in mind that sampling was limited to individuals living in the community and tended to exclude people who had extreme problems with mobility or with self care and therefore likely to be dependent on others for their daily needs. Current investigation of specific patient groups—for example, people attending their general practice surgeries—reveals a wider distribution of reported problems. Thus, to the extent that this survey excluded people who were likely to yield responses indicating more severe problems, the results may well underestimate the health related quality of life of the general population.

Key messages

- Measurement of health outcome requires the observation of states of health
- Patients' involvement in recording and assessing their own state of health is a major element in the process of evaluating the impact of health care
- The EuroQoL EQ-5D questionnaire highlights variations in states of health which are consistent with previously published results
- High degrees of pain are reported in the general population. A category for pain is absent and thus undetected in the survey of disability by the Office of Population Censuses and Surveys

Our data can be treated as descriptive population "norms." As such, they could provide baseline values for monitoring variations in health for specific population groups, particularly if this information was also linked to local epidemiological data. In aggregate form, such information could be used to complement national targets by providing a measure based on health status rather than mortality. The capacity of the EQ-5D questionnaire to generate quantifiable and usable information on the health status of a population led to its inclusion in the 1996 health survey for England.²⁵

Measuring outcomes

However, it is the measurement of change in health status for which the need is greatest. There can be few circumstances in which healthcare workers are not

concerned with the measurement of outcome, and the EQ-5D questionnaire provides the capacity to measure change in health status, and hence outcomes, in a simple standardised way. The information on self reported problems recorded on the first page of the EQ-5D questionnaire identifies a unique health status for which there is a corresponding index value based on the views of the general population.²¹ Changes in health status and the value of that change can be used to quantify outcomes for clinical and economic evaluation; the latter role was recommended for the EQ-5D questionnaire in a report commissioned by the United States Department of Public Health.²⁶ There is "an increasing consensus regarding the centrality of the patient's point of view in monitoring medical care outcomes,"²⁶ and the EQ-5D questionnaire has the obvious potential to contribute to that process. The national survey data reported in this paper show what can be achieved by using an uncomplicated instrument for measuring health status. The further exploitation of its potential is open to us all.

Survey work for the 1993 survey was conducted by Social and Community Planning Research, and we thank the trained field-work staff for their help in the collection of the data.

Contributors: All four authors shared equally in the design and execution of the research reported in this paper. Social and Community Planning Research provided significant additional expertise in the design and management of the national survey. PK will act as guarantor for the paper.

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Conflict of interest: None.

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Appendix

Your own health state today	Your own health state today
<p>By placing a tick in one box in each group below, please indicate which statement best describes your own health state today. Do not tick more than one box in each group.</p> <p>Mobility I have no problems in walking about <input type="checkbox"/> I have some problems in walking about <input type="checkbox"/> I am confined to bed <input type="checkbox"/></p> <p>Self-care I have no problems with self-care <input type="checkbox"/> I have some problems washing and dressing myself <input type="checkbox"/> I am unable to wash and dress myself <input type="checkbox"/></p> <p>Usual activities (eg. work, study, housework, family or leisure activities) I have no problems with performing my usual activities <input type="checkbox"/> I have some problems with performing my usual activities <input type="checkbox"/> I am unable to perform my usual activities <input type="checkbox"/></p> <p>Pain/discomfort I have no pain or discomfort <input type="checkbox"/> I have moderate pain or discomfort <input type="checkbox"/> I have extreme pain or discomfort <input type="checkbox"/></p> <p>Anxiety/depression I am not anxious or depressed <input type="checkbox"/> I am moderately anxious or depressed <input type="checkbox"/> I am extremely anxious or depressed <input type="checkbox"/></p>	<p>To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.</p> <p>We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.</p> <p>Your own health state today</p> <p>Best imaginable health state</p> <p>100 90 80 70 60 50 40 30 20 10 0</p> <p>Worst imaginable health state</p>

EQ-5D questionnaire

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Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study

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Abstract

Objective: To investigate possible associations between use of cardiovascular drugs and suicide. **Design:** Cross sectional ecological study based on rates of use of eight cardiovascular drug groups by outpatients. A population based cohort study including users of drugs to control hypertension. **Subjects:** The ecological study included 152 of Sweden's 284 municipalities. The cohort study included all inhabitants of one Swedish municipality who during 1988 or 1989 had purchased cardiovascular agents from pharmacies within the municipality. Six hundred and seventeen subjects (18.2%) were classified as users of calcium channel blockers and 2780 (81.8%) as non-users. **Main outcome measures:** Partial correlations (least squares method) between rates of use of cardiovascular drugs and age standardised mortality from suicide in Swedish municipalities. Hazard ratios for risk of suicide with adjustments for difference in age and sex in users of calcium channel blockers compared with users of other hypertensive drugs. **Results:** Among the Swedish municipalities the use of each cardiovascular drug group except angiotensin converting enzyme inhibitors correlated significantly and positively with suicide rates. After adjustment for the use of other cardiovascular drug groups, as a substitute for the prevalence of cardiovascular morbidity, only the correlation with calcium channel

blockers remained significant ($r = 0.29$, $P < 0.001$). In the cohort study, five users and four non-users of calcium channel blockers committed suicide during the follow up until the end of 1994. The absolute risk associated with use of calcium channel blockers was 1.1 suicides per 1000 person years. The relative risk, adjusted for differences in age and sex, among users versus non-users was 5.4 (95% confidence interval 1.4 to 20.5).

Conclusions: Use of calcium channel blockers may increase the risk of suicide.

Introduction

A recent epidemiological study reported an excess risk of depression requiring pharmacological treatment after treatment with calcium channel blockers and angiotensin converting enzyme inhibitors but not after treatment with digoxin, anti-arrhythmics, nitrates, diuretics, or β blockers.¹ There have also been case reports suggesting depression²⁻⁵ as well as psychosis⁶ after treatment with calcium channel blockers. As depression may promote suicide we investigated possible ecological associations between suicide rates and the rates of use of eight cardiovascular drug groups in 152 Swedish municipalities. In addition, we investigated the risk of suicide in users and non-users of calcium channel blockers who had purchased prescription drugs mainly used to treat hypertension.

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Methods

This report concerns two different studies: firstly, an ecological study with data from Swedish municipalities on rates of suicide and rates of use of eight groups of cardiovascular drug groups; secondly, the hypothesis generated by this study tested in a cohort study on historical data from users of different antihypertensive drugs.

The ecological study

Sweden is administratively divided into 284 municipalities. Suicide rates for men and women standardised for age for these municipalities during the 5 year period 1989-93 were obtained from the epidemiological centre of the Swedish Board of Health and Welfare. Data on incidence of cause specific mortality were missing for eight municipalities. Data on suicide mortality (ICD-9 (international classification of diseases, 9th revision), codes E950-E959 and E980-E989) were available for 152 municipalities in which the expected number of people committing suicide during the 5 year period was more than five men and five women, as assumed from the overall suicide rates in Sweden.

Rates of use of cardiovascular drugs by outpatients, defined by the Anatomical Therapeutic Chemical (ATC) classification⁷ and expressed as pharmacy dispensed numbers of defined daily doses per 1000 inhabitants per year, were obtained from Apoteks-bolaget (the Swedish Corporation of Pharmacies) for each of the 152 municipalities during each of the years 1989-93. The geometric means of the annual rates of use were used in the calculations.

The rates of use of eight cardiovascular drug groups—diuretics, β blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, lipid lowering agents, low dose aspirin, nitrates, and cardiac glycosides—were correlated with suicide rates by using Pearson's correlation coefficient. Partial correlation coefficients between suicide rates and rates of use of the cardiovascular drug groups were assessed to estimate a correlation coefficient for each drug group independent of variations in the rates of use of the seven other groups to use as a proxy for cardiovascular disease prevalence. All tests were two sided.

The cohort study

Data on individual prescription drug use in a municipality located in mid-eastern Sweden (population about 20 000 in 1989) have been compiled and studied since the 1970s. All prescription drugs purchased by residents from pharmacies within the municipality are registered according to the ATC system.⁷ For the purpose of the present study all inhabitants of the municipality were identified who during 1988 or 1989 had purchased cardiovascular medications with ATC codes (in 1988 and 1989) C02 (centrally acting antiadrenergic agents, ganglion blocking antiadrenergic agents, peripherally acting antiadrenergic agents, calcium channel blockers, angiotensin converting enzyme inhibitors), C03 (diuretics), and C07 (β blockers). ATC codes for calcium channel blockers and angiotensin converting enzyme inhibitors were later changed to C08 and C09, respectively. The subjects were classified as users or non-users of

calcium channel blockers. Mortality data for the cohort until the end of 1994, including the cause of death, were derived from the Swedish mortality register.⁸ Deaths from suicide were defined by the ICD-9 codes E950-E959 and E980-E989. The codes E980-E989 include cases with uncertain intention for suicide. Data on purchased medications and cause of death were linked by the Swedish personal identification number.

Differences in risk of suicide were evaluated by the Kaplan-Meier method and the log rank test. Multivariate adjustments for differences in age and sex were performed with the proportional hazards method. All P values are two sided.

Results

The ecological study

The number of suicides in the 152 municipalities during the 5 year period ranged from 5 to 652. The total number of suicides in the municipalities during this period was 5648. The total population was 7.3 million, and the mean (range) municipality population was 48 042 (13 722 - 679 364) in 1991. Age adjusted suicide rates varied from 0.76 to 3.69 deaths per 10 000 inhabitants per year. The mean (SD) suicide rate for the 152 municipalities was 2.06 (0.49) suicides per 10 000 inhabitants per year. The rates of use were 79.7 defined daily doses per 1000 inhabitants per day for diuretics, 36.8 for β blockers, 22.5 for calcium channel blockers, 20.4 for nitrates, 16.0 for angiotensin converting enzyme inhibitors, 15.3 for cardiac glycosides, 9.4 for low dose aspirin, and 2.9 for lipid lowering agents.

The correlation coefficients for the relations between rates of drug use and rates of suicide are given in table 1. Except for angiotensin converting enzyme

Table 1 Correlation coefficients for rates of use of cardiovascular drug groups and rates of suicide in 152 Swedish municipalities, 1989-93

Drug group	Unadjusted	Adjusted†
Diuretics	0.27**	0.14
β blockers	0.20*	-0.11
Calcium channel blockers	0.36***	0.29***
ACE inhibitors	0.11	-0.09
Lipid lowering agents	0.19**	0.16
Low dose aspirin	0.18*	-0.03
Nitrates	0.17*	-0.12
Cardiac glycosides	0.20*	-0.06

ACE=Angiotensin converting enzyme inhibitors.

†Adjusted for differences in rates of use of all other cardiovascular agents.

*P<0.05; **P<0.01; ***P<0.001.

Table 2 Correlation coefficients for rates of use of calcium channel blockers and rates of suicide in 152 Swedish municipalities, 1989-93

Drug	Unadjusted	Adjusted†
All vasoselective drugs	0.31***	0.21*
Felodipine	0.24**	0.14
Nifedipine	0.21**	0.12
All cardioselective drugs	0.39***	0.17*
Verapamil	0.22**	0.08
Diltiazem	0.28**	0.19*

†Adjusted for differences in rates of use of all agents included in table 1 except calcium channel blockers.

*P<0.05; **P<0.01; ***P<0.001.

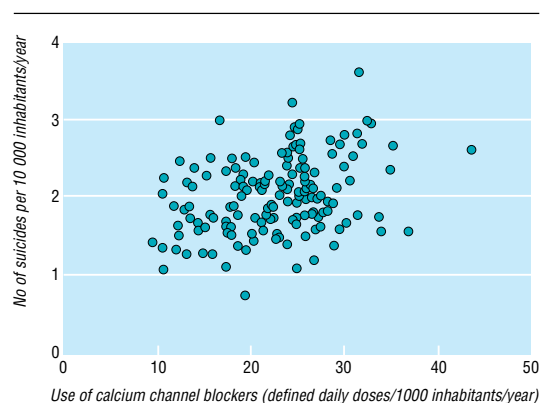


Fig 1 Correlation between rates of use of calcium channel blockers and rates of suicide in 152 Swedish municipalities

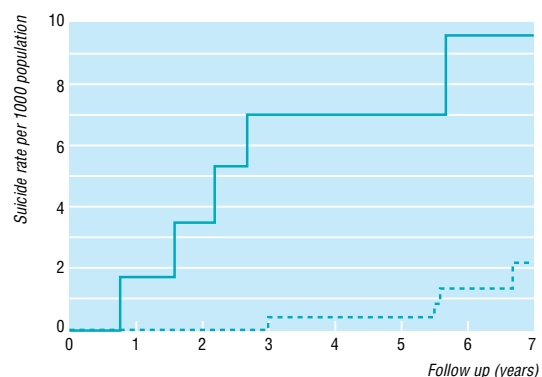


Fig 2 Cumulative rate of suicide over 7 years' follow up in 617 users (continuous line) and 2780 non-users (dotted line) of calcium channel blockers

inhibitors, the rates of use correlated significantly with the suicide rates. The highest correlation coefficient was seen for calcium channel blockers ($r=0.36$, $P<0.001$) (figure 1). After adjustment for differences in the rates of use of the other drug groups, only the rates of use of calcium channel blockers correlated significantly with the suicide rates ($r=0.29$, $P<0.001$) (table 1). Additional adjustment for the proportion of men living in the municipality did not alter this result.

The rates of use of two predominantly cardio-selective and two predominantly vaso-selective calcium channel blockers also correlated significantly with suicide rates (table 2). After adjustment for the rates of use of the seven other types of cardiovascular drug groups, the use of both dihydropyridine and benzothiazepine derivatives remained significantly correlated with suicide rates. When we adjusted for differences in use of the seven other cardiovascular drug groups, the correlation coefficient was 0.21 for dihydropyridine derivatives and 0.18 for benzothiazepine derivatives. The rates of use of diltiazem had the closest correlation with suicide rates (table 2).

The cohort study

In all, 3397 patients were identified as purchasers of drugs with ATC codes C02, C03, and C07 in 1988 and 1989. Of them, 617 (18.2%) were classified as users of calcium channel blockers (nifedipine, verapamil, diltiazem, and felodipine) and 2780 (81.8%) as

non-users. During the follow up, from the date of purchase until the end of 1994, five users of calcium channel blockers (three men and two women, one with uncertain intent) and four non-users (three men and one woman, none with uncertain intent) committed suicide. The 7 year suicide risks were 9.7 and 2.2 per 1000 persons for calcium channel blocker users and non-users, respectively. The difference in suicide risk was significant ($P=0.002$). The average annual absolute risk associated with use of calcium channel blockers was therefore 1.1 suicides per 1000 persons. After adjustment for differences in age and sex the relative risk among users versus non-users was 5.4 (95% confidence interval 1.4 to 20.5). Figure 2 illustrates the cumulative suicide rates during follow up of users and non-users of calcium channel blockers.

Discussion

In the past several groups of cardiovascular drug have been associated with depressive disorders. As suicide is a serious consequence of depression, the current studies were undertaken to evaluate the possible influence of widely used drugs on risk of suicide. The correlation between use of calcium channel blockers and suicide rates found in the ecological study led us to design a cohort study to test if, among users of antihypertensive drugs, subjects using calcium channel blockers had a higher risk of suicide than subjects not using calcium channel blockers.

Diltiazem,² nifedipine,³ and verapamil⁴ have been associated with depressive disorders in case reports and also in a previous epidemiological study that used data on individual prescriptions of calcium channel blockers and antidepressants.¹ The two current studies imply that calcium channel blockers may also promote suicide. In the ecological study the estimated correlation suggests that about one tenth of the intermunicipality variation in risk of suicide is related to the use of calcium channel blockers. In the cohort study the suicide risk in users of calcium channel blockers adjusted for sex and age was fivefold compared with the risk in non-users treated with other antihypertensive agents.

Clinical trials have a limited ability to detect infrequent or late adverse effects or adverse effects resulting in common symptoms. They also often use a number of inclusion and exclusion criteria, thus reducing their generalisability. Studies with a long follow up and studies encompassing the whole population are therefore needed.

In contrast with most clinical trials the current cohort study included all identified users of the study drugs. Consequently the generalisability of the study is high. In the ecological study low populated municipalities with few expected suicides were excluded, so the influence from extreme rates in combination with small number of events was avoided.

In Sweden, as in most other countries, men have a higher incidence of suicide than women. Men are also more likely to be prescribed a calcium channel blocker (unpublished data on file). In our cohort study the estimated rates of suicide were adjusted for differences in age and sex, and, in the ecological study, the suicide rates were adjusted for differences in age. Additional

adjustment of the ecological correlations for the proportion of men in the municipalities did not affect the results (no data given), thus we can eliminate age or sex differences as confounders.

Comorbidity such as cardiovascular diseases might have promoted depressive disorders and suicide. In the ecological study this problem was dealt with by adjusting the correlation for each tested cardiovascular drug group with the rate of use of the seven other drug groups. In the cohort study all subjects were treated with antihypertensive drugs. It follows that although no detailed clinical data were available, users and non-users of calcium channel blockers most probably had similar medical backgrounds.

Populations with a high prevalence of cardiovascular diseases also have a high suicide risk. In the ecological study the rates of use of all but one evaluated cardiovascular drug group also correlated significantly with the suicide rates before adjustment for the rates of use of the other drug groups. After adjustment, however, only the rate of use of calcium channel blockers was significantly and positively correlated with suicide rates (see table 1). Accordingly, the increased suicide risk linked to use of calcium channel blockers would seem independent of cardiovascular comorbidity.

Links with depression

Calcium channel blockers are often prescribed to treat angina pectoris. If angina pectoris causes depression, this might form a link to suicidal behaviour. Nitrates are also prescribed to treat angina pectoris, however, and the rates of use of nitrates did not correlate with suicide rates when we adjusted for the rates of use of other cardiovascular drug groups. Neither did the use of angiotensin converting enzyme inhibitors, often prescribed to patients with diabetes, correlate with suicide rates. Thus, it seems unlikely that the presence of angina pectoris or diabetes help to explain the linking of calcium channel blockers to depression and increased suicide risk.

Other reasons to prescribe calcium channel blockers might have been greater difficulty in achieving control of blood pressure or adverse effects from other antihypertensive drugs. Again, it is not very likely that such circumstances have enough penetrative power to link calcium channel blockers to depression and suicide risk.

In the late 1980s β blockers were suspected of inducing depression.⁹ Therefore, other antihypertensive or antiangina drugs might have been chosen for patients with depression. If calcium channel blockers were used particularly often in depressed patients, an increased suicide risk would appear in users of calcium channel blockers even though the drugs per se would not promote depression and suicide. To behave as a confounder, however, the confounding variable has to be substantially correlated to the tested exposition as well as to the outcome. Therefore, to achieve a high increase in suicide risk by confounding from selective prescribing of calcium channel blockers to depressed patients, most depressed patients with increased risk of suicide and few non-depressed patients should have been prescribed calcium channel blockers. Only about half of depressed patients are correctly diagnosed by their primary care physicians,¹⁰ however, and use of

Key messages

- Clinical trials have a limited ability to detect infrequent adverse effects, so postmarketing reports on adverse effects and observational epidemiological studies are necessary
- The present investigations, including one cross sectional ecological study and one population based cohort study, suggest an increased risk of suicide in users of calcium channel blockers
- The results are in accordance with a depressive effect of calcium channel blockers suggested by case reports and a recent epidemiological study
- Channel blockers should be considered a possible cause of depression and suicide

calcium channel blockers is also obviously common in patients without depression.

In the cohort study population patients were classified as users and non-users of calcium channel blockers at the time of inclusion. Some of the former might have stopped taking calcium channel blockers shortly after inclusion and some non-users might have been prescribed calcium channel blockers after inclusion. Moreover, both studies take drugs purchased from pharmacies into account. It is not certain that each purchased drug was used, and some inhabitants may not have purchased drugs from pharmacies in their home municipality. Provided that the misclassification was independent of the outcome, however, misclassification of exposure would probably have resulted in underestimation of the true association.

One way to interpret the results of the ecological study is to assume that most, if not all, cardiovascular agents have some depressive effect, calcium channel blockers being most prominent. As the studied cardiovascular agents were very heterogeneous, however, a common effect on mood is unlikely.

In contrast with most other cardiovascular agents, calcium channel blockers influence secretory and contractile mechanisms in many different types of cells. Because of their lipophilic properties they easily penetrate the blood-brain barrier. Hence they have access to and may interfere with neurones and receptors involved in the regulation of mood. As calcium channel blockers differ in selectivity and in kinetics their influence on the central nervous system may vary. In the ecological study, however, the rates of use of both dihydropyridine and benzothiazepine derivatives correlated significantly and those of phenylalkylamine derivatives non-significantly with suicide rates after adjustment for the rates of use of other cardiovascular drug groups. Hence it seems likely that calcium channel blockade per se is involved in the increased risk of suicide. A calcium channel effect of dihydropyridines in affective disorders has also been suggested previously.⁵

In conclusion, use of calcium channel blockers may increase risk of suicide. A depressive effect of these drugs has been suggested and may constitute a link with risk of suicide. The consequences of treatment with calcium channel blockers should be further inves-

tigated with respect to depressive disorders and suicide. Calcium channel blockers should be considered as a possible cause of depression and suicide

Contributors: GL initiated the ecological and cohort studies, formulated the study aims, designed the layouts, organised the data collection, and participated in the statistical analysis and interpretation of results and in writing the paper. KB participated in collecting and interpreting results for the cohort study. JR participated in the statistical analysis and interpretation of the data and contributed to writing the paper. LR participated in the interpretation of the data and the writing of the paper. AM, head of the Swedish Network for Pharmacoepidemiology (NEPI), participated in the interpretation of the data and contributed to writing and editing the paper.

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QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin dependent diabetes: cohort study

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Patients with non-insulin dependent diabetes mellitus have an excess risk of dying from cardiovascular disease. One small study suggested that a prolonged QT interval could predict cardiac death in patients with diabetic nephropathy who have received insulin treatment. The question now is whether the same is true in newly diagnosed diabetes in patients who have no apparent complications. In addition, QT dispersion, a new but related electrocardiographic variable, predicts cardiac death in patients who have chronic heart failure, peripheral vascular disease, or essential hypertension.¹⁻³ We investigated whether it also predicted cardiac death in diabetic patients.

Subjects, methods, and results

The study group of 182 patients with non-insulin dependent diabetes mellitus (103 men; mean age 52.8 (SD 8.5) years) represented the Dundee cohort of the United Kingdom prospective diabetes study, which was recruited between 1982 and 1988. Patients were followed up for a mean of 10.3 (1.7) years. The inclusion and exclusion criteria of the study have been reported elsewhere. Patients with overt cardiac disease at baseline were excluded. A single observer (AAON) measured QT intervals as described previously.¹⁻³ Cardiac death was mostly classified at the coordinating centre in Oxford, using the codes of the international classification of diseases, ninth revision. All analysis was done by Cox regression analysis, with cardiac death as the sole end point. We used forward stepwise analysis, each time using all three QT variables along with age, systolic blood pressure, sex, smoking, blood

glucose concentration, and antihypertensive drug. As a result, we identified age, systolic blood pressure, sex, diuretics, and all QT variables as the potentially important variables. Finally we fitted the regression using these four variables with each of the three QT variables.

In those who had a cardiac death, the mean time of death after the baseline electrocardiogram was 7.3 (3.2) years; after the 3 year electrocardiogram it was 4.9 (2.3) years and after the 6 year electrocardiogram 3.8 (1.0) years. The table shows that QTc max, QTc dispersion, and QT dispersion are all highly significant and independent predictors of cardiac death at baseline, at 3 years, and at 6 years. In multivariate analysis they outperformed all other predictors.

Comment

Our main finding was that QT dispersion, QTc dispersion, and QTc max are excellent predictors of cardiac death in patients with non-insulin dependent diabetes mellitus. QTc interval analysis has two major advantages over other possible ways of stratifying risk in patients. Firstly, measurements of QTc interval are easily obtained with a non-invasive routine test: other potential predictors of cardiac death often require extra testing with specialised equipment. Secondly, comparisons between QTc dispersion and micro-albuminuria suggest that QTc dispersion is a better predictor of cardiac death.⁴ A QTc dispersion > 78 ms at year 6 in this study had 100% sensitivity and 90% specificity, giving an odds ratio of 9.0, whereas the odds

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Cox multivariate regression analysis for prediction of cardiac death from data at various time points

	B	SE	Wald χ^2 statistic	P value
Baseline				
QTc dispersion	0.021	0.0069	9.40	0.002**
Age	0.080	0.0312	6.61	0.010*
Systolic blood pressure	0.016	0.0080	4.16	0.041*
Sex	0.682	0.5130	1.77	0.183
QT dispersion	0.018	0.0068	7.07	0.008**
Age	0.075	0.0314	5.74	0.017*
Systolic blood pressure	0.016	0.0081	3.96	0.047*
Sex	0.534	0.5016	1.13	0.287
QTc max	0.0166	0.0042	15.45	0.0001**
Age	0.0699	0.0322	4.69	0.0303*
Sex	1.143	0.5269	4.71	0.0300*
Systolic blood pressure	0.0139	0.0077	3.27	0.0707
Year 3				
QTc dispersion	0.017	0.0074	5.15	0.023*
Systolic blood pressure	0.019	0.0118	2.58	0.108
Age	0.046	0.0371	1.51	0.219
Sex	0.569	0.6090	0.87	0.351
QT dispersion	0.018	0.0070	6.46	0.011*
Systolic blood pressure	0.018	0.0115	2.46	0.117
Age	0.045	0.0370	1.48	0.225
Sex	0.539	0.6004	0.80	0.372
QTc max	0.017	0.0054	9.79	0.002**
Sex	0.910	0.6440	2.00	0.157
Age	0.051	0.0380	1.85	0.174
Systolic blood pressure	0.015	0.0117	1.63	0.202
Year 6				
QTc dispersion	0.036	0.0113	10.29	0.001**
Sex	1.667	0.9790	2.90	0.089
Age	0.034	0.0610	0.31	0.575
Systolic blood pressure	0.000	0.0160	0.00	0.986
QT dispersion	0.024	0.0105	5.37	0.020*
Sex	1.219	0.8530	2.04	0.153
Age	0.050	0.0540	0.87	0.351
Systolic blood pressure	0.003	0.0160	0.04	0.838
QTc max	0.035	0.0110	10.36	0.001**
Sex	1.827	0.9210	3.94	0.047*
Age	0.038	0.0540	0.51	0.477
Systolic blood pressure	0.015	0.0190	0.599	0.439

*P<0.05, **P<0.005. Although diuretics were significant in univariate analysis, they were not significant in multivariate analysis.

ratio for microalbuminuria was only 1.8 in a recent overview.⁵

The question arises why analysis of QT interval should be able to predict cardiac death. QT dispersion may be a composite term reflecting electrical inhomogeneity as a result of ischaemia, left ventricular dilatation, left ventricular hypertrophy, cardiac fibrosis, and autonomic neuropathy. Each one of these individually confers increased cardiac risk, and this may be why QT dispersion, as a composite of them, is highly predictive of cardiac death. The clinical value of analysing the QT interval may therefore be that it could be used as a screening test to select diabetic patients for more extensive cardiac investigations. Importantly, the time between measuring a prolonged QT interval and the subsequent cardiac death is many years, which provides ample opportunity to intervene.

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How often does surgery for peptic ulceration eradicate *Helicobacter pylori*? Systematic review of 36 studies

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continued over

BMJ 1998;316:746-7

Most peptic ulceration is due to chronic infection with *Helicobacter pylori*, and antibiotic treatments can generally cure both the infection and the ulceration.¹ In previous decades, however, persistent peptic ulceration was often treated surgically either by vagotomy, which merely reduces symptoms, or by partial gastrectomy, which removes the ulcer and parts of the stomach likely to be infected with *H pylori*.² There have been several surveys on the prevalence of persistent *H pylori* infection in patients who have undergone surgery for peptic ulceration, often many years previously. We present a systematic review of these surveys and

compare the type of surgery with the likelihood of persistent *H pylori* infection.

Methods and results

We checked in databases, reference lists, and gastroenterology journals for any studies published before January 1997 that assessed *H pylori* infection after surgery for peptic ulceration. Studies were included if they provided information on the indication for surgery and the type of surgery. We tabulated the type of surgery, the mean interval between surgery and testing

for *H pylori* (average 10 years), the method of testing for *H pylori* (mostly histology), the site and number of gastric biopsies, and the prevalence of infection. Among the 33 reports identified we excluded five: one included unrepresentative patients (*Hepato Gastroenterol* 1994;41:542-5), and four did not provide separate results for patients with peptic ulceration (*Helicobacter* 1996;1:270; *Z Gastroenterol* 1993;31:115-9) or patients who had had partial gastrectomy (*Surg Gynecol Obstet* 1993;176:594-8; *Mat Med Pol* 1994;88:13-6). From 28 publications, 36 studies were included. Prevalences from different studies were combined by direct summation of their numerators and denominators. The results from the small studies—that is, those with fewer than 20 patients—were combined in the figure and when displaying the results from separate studies and calculating standard χ^2 tests of heterogeneity.

Among patients who had undergone vagotomy alone the prevalence of persistent *H pylori* infection was about 83% (542/656), whereas for partial gastrectomy it was only about 50% (292/580; figure). There were insufficient data to compare the prevalence of *H pylori* infection after particular types of partial gastrectomy—for example, Billroth *v* Roux-en-Y—or vagotomy—for example, highly selective *v* truncal. The heterogeneity within the two subtotals ($\chi^2_{12}=47$ and $\chi^2_8=14$) was much less extreme than the heterogeneity between the two subtotals ($\chi^2_1=147$, $P<0.0001$). Thus the difference in prevalence between the subtotals remained informative.

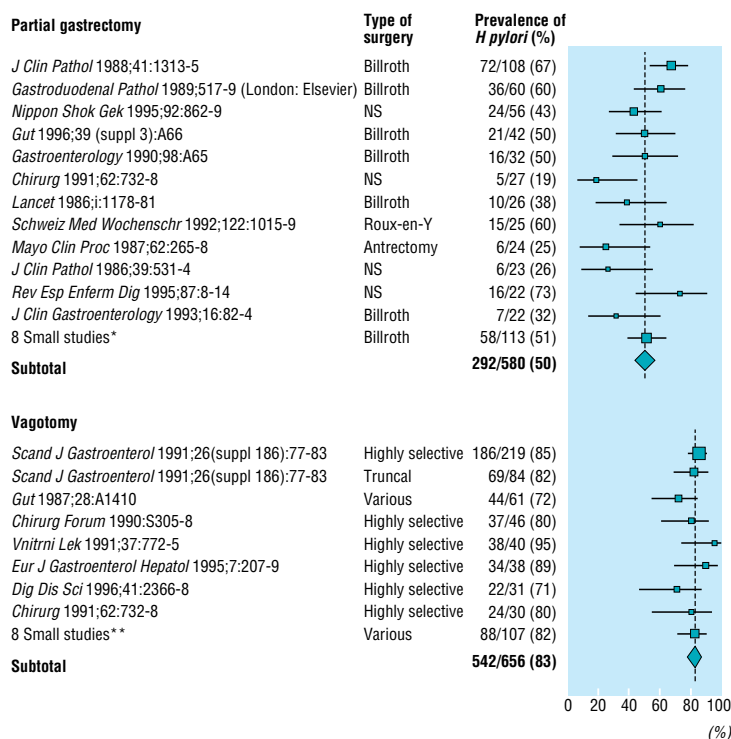
Comment

Other studies have shown that most patients with active peptic ulcers are infected with *H pylori*—about 95% of those with duodenal ulcer and 85% of those with gastric ulcer.³ The prevalence of *H pylori* in such patients remains high after vagotomy (83% (95% confidence interval 78% to 86%)) but falls to about 50% (45% to 56%) after partial gastrectomy. This difference cannot be explained by the methods used for testing for *H pylori* or for gastric tissue sampling as both were similar across studies, or by differences in reinfection rates postoperatively. Despite the inclusion of studies reported as abstracts or in languages other than English some publication bias may remain, although this should not alter the main conclusions. Remission of *H pylori* infection after partial gastrectomy may be due partly to the resection of distal gastric tissue, a usual site of infection, and partly to the bactericidal effects of prolonged bile acid reflux in surgical patients.⁴ Whatever the reason, this decrease represents one way surgery could contribute to the cure of peptic ulcer disease.

The main clinical implication of the persistently high prevalence of *H pylori* infection postoperatively is that patients who have undergone gastrectomy or particularly vagotomy should be reviewed and considered for antibiotic treatment that will cure their chronic infection.

Carsten Flohr, Sumiyo Iida, and Monika Jakubiec helped with translations.

Contributors: JD is guarantor; he also initiated the study, identified and abstracted information from publications, performed statistical analyses, interpreted the data, and drafted



Prevalence of *Helicobacter pylori* after surgery for peptic ulcer: 36 studies. Size of black area proportional to number of patients. NS = not specified (**Dig Dis Sci* 1991;36:1697; *J Clin Gastroenterol* 1993;16:82-4; *Gastroenterology* 1989;96:A247; *Mat Med Pol* 1994;88:9-12; *Gastroenterology* 1989;97:958-64; *Ann Chir* 1991;45:905-8; *Gut* 1989;30:1552-7; *Pol Arch Med Wewn* 1991;86:13-7. ***Lancet* 1986;1:1178-81; *Gastroenterology* 1989;97:958-64; *Gastrointestinal pathology and Campylobacter pylori* (London: Elsevier) 1989: 517-9, 525-7; *Ann Chir* 1991;45:905-8; *Zentralbl Chir* 1995;120:364-72; *Gastroenterology* 1990;98:A65; *Mat Med Pol* 1994;88:9-12)

the report. PA plotted the findings, discussed statistical issues, and edited the report. RP provided the statistical methods, interpreted the data, and drafted the report.

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Conflict of interest: None.

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Corrections

Birth weight and cognitive function in young adult life: historical cohort study

An authors' error occurred in this paper by Henrik Toft Sørensen et al (16 August, pp 401-3). The correct mean (SD) score for parity should have been 0-1: 43.6 (9.4); 2: 42.2 (9.7); ≥ 3 , 41.0 (10.1). These values did not lead to any errors in the risk calculations, and there were no consequences for any of the results.

Childhood energy intake and adult mortality from cancer: the Boyd Orr cohort study

An editorial error occurred in this paper by Frankel et al (14 February, pp 499-504). In table 5 the third cause of death under each of the three main headings (Both sexes, Men, and Women) should have read: Cancers not related to smoking [not Cancers not related to cancer, as published].

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<http://content.nejm.org/cgi/content/full/347/2/81>

8- Did you know -That only about [one person in 13 treated with an Epidural injection](#) for Chronic back pain or Sciatica will experience sustained relief of more than half there pain brought upon by this injection?

9- Did you know -That only about [one person in 6](#) treated with Cymbalta for Chronic Nerve pain or Fibromyalgia will experience relief of more than half there pain brought upon by this medication? [One in 11 will have to stop the drug because it harms them.](#)

10- Did you know -[That only one person in 4 treated with Lyrica](#) for Chronic Nerve pain will experience relief of more than half there pain? [For fibromyalgia , it is only one in 6.](#) For either, about one in 12 will have to stop the drug because it harms them.

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ד"ר אדהאן. "מי שלוקח תרופות כמו אקמול או נורופן על בסיס קבוע, עלול לגרום לעצמו כאבי ראש"

ד"ר חיים משה אדהאן מנוף איילון מפעיל את מרפאת הכאב החדשה שנפתחה במודיעין • חמוש במכשירי לייזר, אלקטרוניקה לא פולשנית וכיפה על הראש, הוא מציע לכל מי שרוצה לדלג על התרופות הרגילות לעבור ישר לפלאי הטכנולוגיה

חנה שטרן

בשנת 2005 עלה ד"ר חיים משה אדהאן לישראל מקנדה עם ספר תהילים בידו. שם, ביבשת בה גדל, היה מומחה לרפואת משפחה ורפואת ספורט ועבד, בין השאר, גם בקרב הקהילה האסקימוסית. הוא ניהל מרפאת כאב, בה הועסקו 54 עובדים ופקדו אותה כאלף מבקרים בשבוע.

ד"ר אדהאן, בן 45 שעסק בעיקר במחקר, הגיע לפני כשנתיים גם לבית החולים תל השומר, שם הוא מנהל כיום את מרפאת הכאב. הוא חובש כיפה ומקיים

מצוות, עטור בזקן ג'ינג'י, אופטימי וחייכן, ומודה שהוא די מרוצה בארץ הקודש. את רוב הראיון הוא מעדיף לנהל באנגלית. יש לזכור, כי מדובר בעולה חדש יחסית, דובר עברית בסיסית של אולפן. ד"ר אדהאן הוא אב לשישה ילדים, שהקטן בהם רק בן שלושה חודשים. הוא נשוי לתמר, רופאת שיניים, ומתגורר בישוב הצמוד למודיעין - נוף איילון.

ישראל עדיין מאחור

בחודש יולי נפתחה במודיעין מרפאה לטיפול בכאבים, במסגרת מרפאת "טרם" ברחוב תלתן. את

הטיפולים המקצועיים הוא מעניק לחולים שהתרגלו לקחת טיפול תרופתי, ליטול משככי כאבים ולקבל זריקות. ד"ר אדהאן אומר כי מדובר בבשורה ובגילוי, כי מעבר לפתרון הרפואי המקצועי, הכולל תרופות שונות וזריקות להקלה על הכאב, יוכלו להיעזר גם במכשירים טכנולוגיים חדשניים שמסוגלים לפתור בעיות כאב שונות. "יותר אנשים מתים מתופעות לוואי של תרופות אנטי דלקתיות. זה הורג יותר ומתאונות דרכים או פיגוע", טוען ד"ר אדהאן.

איך מתבצע הטיפול אצלך בשונה מרופאים אחרים?

"היה סטארט-אפ ישראלי של מכשיר שרלוונטי

לתחום הכאב, אבל השימוש הראשוני במכשיר היה למטרה אחרת של מניעת דלקת לאנשים שיש להם קטטר. הממציאים שמו לב שמי שנעזר במכשיר אחרי הניתוח, לא סבל מכאבים. המרכז שלי עסק במחקרים על כאב, וידעו שאני מבין בתחום. לאחר שבדקתי את המכשיר ומה ניתן לעשות בו הכי טוב, הגעתי לפריצת דרך: זה לא רק מפסיק את הכאב, אלא גם מרפא. למדתי שישראלים סובלים יותר מאשר אנשים המתגוררים באיחוד האירופי, אך הטיפול בארץ בכאב הוא תחום חדש. לרופאים כאן אין תמיד את

"רוב המטופלים שמגיעים אלי ראו כבר הרבה מומחים, כולל מומחים לכאב. הם מתפללים שאפשר לעזור להם. הם חושבים בדרך כלל שעליהם ללמוד ולהתרגל לחיות עם הכאב. הם שמחים לראות שאפשר לטפל בהם"

הזמן לברר מהיכן הכאב. המטופל מגיע לביקור קצר אצל הרופא שלא יכול לטפל בחולה בחמש דקות. כאשר אני מקבל חולה חדש, אני מקדיש לו כשעה כדי לחקור מאיפה הכאב נובע, מתי הוא מגיע, מה משפר את המצב ומה גורם ליותר כאב. הייתי בשוק שהתחלתי לעבוד כאן, איך הכאב מטופל".

באיזה סוג של כאבים אתה יכול לטפל?

"בבעיה נוירולוגית, כמו של מיגרנות, כאב בפרצוף. לדוגמה: אני עובד עם אשתי (רופאת שיניים) על כאבי שיניים של מטופלים אחרי פגיעה בלסת או בכאבים אורטודיים, פגיעה בגיד, בכאבי גב תחתון".

איך המכשירים, שאתה נעזר בהם פועלים להקלת הכאב?

"יש מכשיר הנקרא 'פיינשילד' (בתרגום: מגן כאב - ח.ש) שקיים בשוק כשנה, וטיפולי באמצעותו כבר במאה חולים. המכשיר שווה במקביל גם באירופה ובארה"ב. למכשיר מחוברת מדבקה. רוב המטופלים לוקחים את המכשיר, שמים את המדבקה במקום של הכאב והולכים לישון איתו לדוגמה, לשמונה שעות. אפשר להשתמש בו גם בשעות היום, ואפשר להסתיוב איתו גם לזמן של שמונה שעות. זמן הטיפול תלוי בסוג הבעיה וגם בגיל המטופל. מי שצריך כמו שחקן כדורסל, זה אורך שלושה שבועות. למבוגרים יותר, לוקח יותר זמן, חודשים ולא שבועות.

"יש גם מכשיר לטיפול באמצעות קרני לייזר. מדובר במכשיר עם 30 שנות ניסיון של מחקר. ניתן לטפל באמצעותו במיגרנות, כאבי צוואר, גב תחתון וכאבי מפרקים. הוא בטוח ללא תופעות לוואי. אשתי, המשך בעמ' 96 <

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מסדר חשמלי להפגת כאב. אפשר גם לשכור או לקנות

לעזור להם. הם חושבים בדרך כלל שעליהם ללמוד ולהתרגל לחיות עם הכאב. הם שמחים לראות שאפשר לטפל בהם. אנשים לא צריכים להתייחס בגלל כאבים. זה לא רע, אבל יש מקרים שזה גורם להם למוגבלות. הכאב זה הסיבה הראשונה בארץ ובעולם המערבי למוגבלות, במיוחד כאבי גב תחתון. יש גם טיפול במגרנות באמצעות ליזור, ללא תופעות לוואי או תרופות. מי שלוקח תרופות, כמו אקמול או נורופן על בסיס קבוע, או תרופות אנטי דלקתיות, עלול לגרום לעצמו כאבי ראש...".

מה ההבדל בין הטיפול שניתן כאן בעיר לבין בית החולים?
"בתל השומר יש המתנה של כארבעה חודשים, כאן אין, ויש כאן את הציוד שלי. קיבלתי בקשה ממרפאת 'טרם' שיש אנשים סובלים, שצריכים לקבל שירותים בקופה, ויש המתנה ארוכה. לכן החלטתי לפתוח גם כאן סניף למרפאת כאב".

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מפרק, או אכלה סטובלים מפברומיאלגיה (תשישות כרונית), כאבי צוואר, פגיעות עצבים שברים או נקעים. בטיפול במכשיר הלייזר, תוך שבועיים מרגישים יותר טוב, למי שסובל מבעיות כרוניות במקום לקחת תרופות. מדי פעם אפשר להפסיק לקחת תרופות לאחר טיפול בלייזר. המכשירים עובדים יותר מאשר תרופות, לדוגמה: באמצעות לקחת תרופה - ירידה של 30 אחוזים, ואילו באמצעות הטכנולוגיה - ירידה של 50 אחוזים. יש גם אחיזי של שברים וריפוי מהיר יותר אם משתמשים במכשיר ה'פיינשילד'. זה לא רק כואב פחות, אלא מרפא בצורה יותר סולידית, כמו אנשים מבוגרים שסובלים מבריתת סידן - אוסטאופורוזיס. לכאב צוואר או כאב גב תחתון, אני משתמש בלייזר יותר מאשר באולטרסאונד. ההסתייגות היחידה היא שאני לא מטפל בילדים אלא רק מתחיל מעל לגילאי 16".

מי מגיע אליך? מה הכאב הנפוץ ביותר?
"רוב המטופלים שמגיעים אלי ראו כבר הרבה מומחים, כולל מומחים לכאב. הם מתפלאים שאפשר

לדוגמא, כאשר הייתה בהריון בחודש תשיעי, היו לה כאבי גב תחתון, ואי אפשר היה לקחת תרופות, אבל אפשר להשתמש במכשיר הלייזר, למצוא ארבע נקודות בגב ולהקרין עליהן, במשך שש דקות על כל נקודה, פעמיים ביום. הבעיה נעלמה ב-80 אחוזים. גם למבוגרים עם בעיות כרוניות כדאי לנסות. אי אפשר להבטיח שמוחקים את הכאב לגמרי אלא גורמים רק להקלה חלקית".

האם מדובר בטיפול יקר או שווה לכל נפש? מה ההבדל בין שני המכשירים?

"אפשר לשכור או לקנות את מכשיר ה'פיינשילד'. לא מקבלים על זה עדיין החזר מקופות החולים. לשכור את המכשיר עולה 650 שקלים פלוס 165 שקלים למדבקות. זו רק טכנולוגיה אחת. אפשר לשכור גם את מכשיר הלייזר שנראה ממש כמו מכונת גילוח קטנה".

הקלה תוך שבועיים

כמי מטפלים במסגרת מרפאת הכאב בבית החולים? למי זה עוזר?

"לבית החולים מגיעים חייילים, פגועי חוט שדרה, מקרי קטיעות, פגיעות ראש שיש להם כאבים בלתי נסבלים. שליש מהחולים שלי הם חולים שעברו פציעות מכל המלחמות. אנו מטפלים בהם בשיטה רב מקצועית. יש לנו פיזיותרפיסטים, אחיות, מרפאים בעיסוק, מרפאים באמנות, יוגה עובדים סוציאליים ופסיכולוגים. אנו מטפלים גם באזרחים שעברו תאונות דרכים, או אכלה שעברו ניתוחי גב או

איך זה עובד?

(תדירות של 20-120 קילוהרץ ועוצמה של 0.4-1 וואט) מוכר במחקר הרפואי כאמצעי יעיל לשיכוך כאבים ולטיפול בפציעות, בקרעים בגידים או בעצבים פגועים. שימוש ב"פיינשילד" לטיפול ממושך של כמה שעות ביום נמצא יעיל יותר משימוש במכשירים סטנדרטיים, שמספקים אולטרסאונד בתדירות ובעוצמה גבוהות ומוגבלים, משום כך, בשימוש לפרקי זמן קצרים בלבד.

ד"ר אדהאן מציג למטופלים שיטות שמרגינות נוספות כאלטרנטיבה לטיפול בכאב. הוא בעל תואר מטעם האקדמיה הקנדית לרפואת ספורט וכן בעל תואר מומחה ברפואת שיקום מקנדה ומארה"ב טרם עלייתו ארצה. לד"ר אדהאן ניסיון בטיפול בכאב בחולים שהרפואה הקוננוציונאלית לא גרמה לשיפור במצבם. המוטו של ד"ר אדהאן: "איכות החיים שלך ראויה להשקעה. הונחה וניהול לקוי של הטיפול בכאב ישפיעו לטווח הארוך על בריאותך, הן מבחינה פסיכולוגית והן מבחינה פיזית ותפקודית".



מטופל בתהליך. לייזר יחד עם טיפול בגלי הלם את מצבם של החולים. הצלחות דומות דווחו בטיפול בחולים שסבלו מכאבים ממקור עצבי, כמו חולי שלבכת חוגרת או אנשים שסבלו מפגיעה בעצב בעקבות טראומה או קטיעה. אולטרסאונד טיפולי בתדירות ובעוצמה נמוכות

מדובר במתמר אולטרסאונד זעיר שקוטרו כשני סנטימטרים, המובנה בתוך מדבקה. המתמר מקושר ליחידת בקרה אלקטרונית נישאת, בממדים של טלפון נייד. המדבקה ממוקמת באזור הטיפול ומפיקה גלי אולטרסאונד, ובאמצעותה יכולים חולים לקבל טיפול ממוקד וממושך (עד כשמונה שעות טיפול).

גלי האולטרסאונד שמפיק המתמר מתפשטים על שטח של כ-20 סנטימטרים וחודרים לעומק של כארבעה סנטימטרים ברקמה רכה (התדירה עמוקה יותר אם המכשיר פועל על רקמת עצם). הגלים יוצרים לחץ מכני באזור הפגוע, המשפר את זרימת הדם באזור הפגוע ואת יכולתם של התאים לקלוט חומרים המסייעים לריפוי, והוא גם מגביר ייצור טבעי של חומרים התורמים לשיכוך כאב. לצד המדבקה, נעשה שימוש במשחת "קטמין", שנמרתה על האזור הפגוע. לדברי ד"ר אדהאן, האולטרסאונד הפחית משמעותית את רמת הכאב וגם עזר להתדרת המשחה לעור, וכך סייע לשפר

ד"ר אדהאן נעזר בשתי טכנולוגיות נפרדות לטיפול בכאבים: האחת - טכנולוגיית האולטרס-אונד בתדר נמוך לטיפול בכאב, והשנייה - שימוש במכשיר לייזר יחד עם טיפול בגלי הלם (Shock Wave Therap).

הוא מדרך את המטופלים לאחר פגישת מקדימה ואבחון מהות הכאב, בבחירת הטיפול המתאים מתוך מגוון האפשרויות הקיימות, החל מהשיטות הקוננוציונאליות והשמרגיות, דרך טיפולים כירורגיים וכלה בטיפולים משלימים. המטופלים יכולים לשכור את המכשיר ולעשות בו שימוש עצמי במידה ויחליטו לרכוש את המכשיר. מחיר ההשכרה מורד ממחיר המכשיר.

מהו מכשיר ה"פיינשילד"? הטכנולוגיה שבה פועל ה"פיינשילד", שפותחה על ידי חברת הסטארט-אפ הישראלית "ננוויברוניקס", מאפשרת לגלי הקול לעבור דרך הגולגולת ולטפל בעצב המשולש, דבר שאינו אפשרי במכשיר האולטרסאונד הסטנדרטי.

The Pain Treatment Center

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