

Volume 165

April 2001

Number 4

Full Text Online Access Available
jurology.com

The Journal of UROLOGY®

Official Journal of the American Urological Association, Inc.®
Founded In 1917 By Hugh Hampton Young



WESTON LIBRARY

MAR 19 2001

J5/120 CLINICAL SCIENCE CENTER
600 HIGHLAND AVE MADISON WI 53792

Annual Meeting, American Urological Association, Inc.®, Anaheim, California, June 2-7, 2001

Cala Health Ex. 1005
Cala v. EMKinetics
USP 9,287,338

The Journal of UROLOGY®

Editor

Jay Y. Gillenwater
1120 North Charles Street
Baltimore, Maryland 21201

Associate Editors

Jean B. deKernion
Los Angeles, California

Edward J. McGuire
Ann Arbor, Michigan

Section Editors

Jack S. Elder
Cleveland, Ohio

Anthony Atala
Boston, Massachusetts

Ralph V. Clayman
St. Louis, Missouri

Editorial Board

Mid-Atlantic

Burkhardt H. Zorn
Washington, D. C.

New England

Kevin R. Loughlin
Boston, Massachusetts

New York

Carl A. Olsson
New York, New York

North Central

Robert C. Flanigan
Maywood, Illinois

Drogo K. Montague
Cleveland, Ohio

Northeastern

William C. Hulbert, Jr.
Rochester, New York

South Central

H. Barton Grossman
Houston, Texas

Southeastern

Joseph A. Smith, Jr.
Nashville, Tennessee

Jerry W. Sullivan
New Orleans, Louisiana

Western

Donald E. Novicki
Scottsdale, Arizona

Brent W. Snow
Salt Lake City, Utah

Board of Consultants

David G. Bostwick
Rochester, Minnesota

Lance K. Heilbrun
Detroit, Michigan

Charles Y. C. Pak
Dallas, Texas

Michael B. Cohen
Iowa City, Iowa

Michael W. Kattan
New York, New York

Derek Raghavan
Los Angeles, California

Fred Dorey
Los Angeles, California

Steven A. Leibel
New York, New York

Arthur T. Rosenfield
New Haven, Connecticut

Robert Elashoff
Los Angeles, California

Seth P. Lerner
Houston, Texas

Deborah S. Smith
New Haven, Connecticut

Jonathan Epstein
Baltimore, Maryland

Ronald R. Townsend
Denver, Colorado

Former Editors

Hugh H. Young
1917-1945

J. A. Campbell Colston
1946-1965

Hugh J. Jewett
1966-1977

William W. Scott
1977-1983

Herbert Brendler
1983-1985

John T. Grayhack
1985-1994

The Journal of Urology® (ISSN 0022-5347) is the Official Journal of the American Urological Association, Inc.®, and is published monthly by Lippincott Williams & Wilkins, 12107 Insurance Way, Hagerstown, MD 21740. Business offices are located at 227 East Washington Square, Philadelphia, PA 19106-3780. Periodicals postage paid at Hagerstown, MD, and at additional mailing offices. Subscription rates individual \$401.00 (\$501.00 foreign); institutions \$442.00 (\$542.00 foreign); in-training \$224.00 (\$308.00 foreign); add \$35.00 for air freight delivery outside of North America. All subscription rates include access to The Journal of Urology® Online (jurology.com); single copy \$47.00. Foreign prices exclude Japan (See Information for Subscribers). Printed in USA.

Subscription prices subject to change. The GST number for Canadian subscribers is 89552 4239 RT. To order call 1-800-638-3030 from anywhere in the U.S. Outside North America, call 301-714-2300 or fax 301-824-7390. POSTMASTER: Send address changes to: Lippincott Williams & Wilkins, 12107 Insurance Way, Hagerstown, MD 21740. Indexed by Index Medicus (abridged), Current Contents, Clinical Medicine, Life Sciences, Science Citation Index, Research Alert, ISI/BioMed, EMBASE/Excerpta Medica, BIOSIS, and Reference Update. On-line text is available through Ovid Technologies, Inc. and directly from the publisher at jurology.com. Printed on acid-free paper. Copyright © 2001 by American Urological Association, Inc.®

PERCUTANEOUS AFFERENT NEUROMODULATION FOR THE
REFRACTORY OVERACTIVE BLADDER: RESULTS OF A MULTICENTER
STUDYFRED E. GOVIER, SCOTT LITWILLER, VICTOR NITTI,* KARL J. KREDER, JR.†
AND PETER ROSENBLATT*From the Virginia Mason Medical Center, Seattle, Washington, University of Texas Southwestern Medical Center, Dallas, Texas, New York University Medical Center, New York, New York, University of Iowa Hospitals and Clinics, Iowa City, Iowa, and Mt. Auburn Hospital, Cambridge, Massachusetts*

ABSTRACT

Purpose: More than 20 million Americans have an overactive bladder, the predominant symptoms being frequency, urgency, urge incontinence and pelvic pain. While the etiology is not completely understood, most investigators believe the causes to be many and the pelvic floor to be intimately related. Whatever the etiology, traditional therapies, including dietary manipulation, bladder drill, medications and physical therapy, are often poorly tolerated and/or ineffective. We report a prospective, multicenter clinical trial that was undertaken to determine the safety and efficacy of percutaneous peripheral afferent nerve stimulation for treatment of refractive overactive bladder and/or pelvic floor dysfunction.

Materials and Methods: A total of 53 patients with overactive bladders, in whom all traditional therapy failed, were enrolled in 1 of 5 sites within the United States. Patients received weekly percutaneous electrical stimulations via a 34 gauge needle placed near the tibial nerve 3 finger breadths above the ankle. Urodynamic studies, detailed voiding diaries, quality of life surveys, and incontinence impact questionnaires were completed before, during and after the study.

Results: Of the patients with a mean age of 57.4 years 89% (47 of 53) completed the 12-week study. A total of 71% of patients were classified as treatment successes by the investigators and were started on long-term treatment. On average patients noticed a 25% reduction in mean daytime and 21% reduction in mean nighttime voiding frequencies ($p < 0.05$). Urge incontinence was reduced by an average of 35% ($p < 0.05$). Statistically significant improvements were noted in selective pain and quality of life indexes. No significant adverse events related to treatment were noted in any patients.

Conclusions: Percutaneous peripheral afferent nerve stimulation offers a safe, minimally invasive and effective treatment for managing refractive overactive bladder and/or pelvic floor dysfunction.

KEY WORDS: neurotransmitters, bladder, multicenter studies

The physiology and neuroanatomy of the pelvic floor and detrusor mechanism are complex and incompletely understood.¹ Yet the typical urologist sees and treats disorders of these complex systems on a daily basis, often with limited success. While a variety of diagnoses are made, some of the most common symptoms for which our patients seek our help are voiding frequency, urgency, urge incontinence and pelvic pain. After a thorough detailed evaluation ruling out infection, malignancy and structural abnormality, a significant portion of this group remains undiagnosed. Urologists then move to dietary manipulation, bladder drill, medical therapy and pelvic floor rehabilitation, and again a significant number of patients will have bothersome and sometimes debilitating symptomatology, which frustrates patients and physicians alike.

To our knowledge interest in direct electrical stimulation of

Accepted for publication October 13, 2000.

*Financial interest and/or other relationship with Abbott, Boehringer Ingelheim, Merck, Pfizer, Pharmacia Upjohn, Protein Technologies, Schwarz Pharma and UroSurge, Inc.

†Financial interest and/or other relationship with Merck, Pharmacia Upjohn, UroSurge, Inc. and Zeneca.

Editor's Note: This article is the fifth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1264 and 1265.

the detrusor began in the 1950s.² The 1960s brought further understanding and attempted to influence voiding via stimulation of the pelvic³ and sacral nerves.^{4,5} The detailed work of Tanagho and Schmidt in the 1970s and 1980s⁶ paved the way for a randomized, prospective multicenter study on sacral stimulation, which was initiated in 1993. This study involved 76 patients with refractory urge incontinence who responded to test stimulation of the sacral nerve roots. A total of 34 patients received a permanent implant and 42 received standard medical therapy. At 6 months the severity, frequency and number of pads used for incontinence were dramatically reduced in patients who received an implant. Of the implanted group 47% were completely dry and an additional 29% demonstrated a greater than 50% reduction in incontinence episodes. Unfortunately, pain was encountered at the generator site in 15.9% of patients and at the implant site in 19.1%. Lead migration occurred in 7%, and surgical revisions were required in 32.5% of patients.⁷

To our knowledge direct electrical stimulation of the tibial nerve was first reported by McGuire et al in 1983.⁸ Of 22 patients with urge incontinence 12 (55%) were dry and 7 (32%) had improvement after electrical stimulation via a stick on electrocardiogram type electrode with foam backing. In 1987 Stoller et al reported that intermittent peripheral

stimulation of the tibial nerve in pig-tailed monkeys could inhibit bladder instability and urge incontinence.⁹ Stoller began treating patients in 1987 and recently submitted his results in 98 patients treated with intermittent percutaneous stimulation of the tibial nerve during a 10-year period at University of California, San Francisco (personal communication). His work resulted in the current, prospective multicenter clinical trial to determine the safety and efficacy of percutaneous tibial nerve stimulation for refractory overactive bladder and/or pelvic floor dysfunction.

MATERIALS AND METHODS

A total of 53 patients were enrolled during a 12-month period in a prospective, multicenter clinical trial (see table). Our primary objectives were to demonstrate the safety and efficacy of the percutaneous Sans[‡] device for treatment of refractory overactive bladder and/or pelvic floor dysfunction. Change in mean daytime voiding frequency from baseline to 12 weeks was defined as the primary efficacy end point. Mean voiding frequency at weeks 0 (baseline), 4, 8 and 12 was determined for each patient using a 3-day voiding diary. The primary safety end point was defined as a composite event comprised of moderate to severe pain, objective evidence of infection or device malfunction.

Our secondary objectives were to characterize the multidimensional nature of the effects of modulation, focusing on the impact treatment might have on patient episodes of urge incontinence and pelvic pain. This process was done by examining reported changes with time in the symptoms and impact of incontinence on health related quality of life from baseline to 12 weeks. A number of symptom measures and quality of life indicators were used. Tertiary objectives of our study were to examine the maximal interval of efficacy maintenance for patients on the tapering protocol after discontinuation of weekly therapy at the end of the initial 12-week period. Patients were followed with a patient specific treatment protocol as a means to determine the maximal interval of efficacy maintenance.

All patients gave a complete history, underwent a physical examination and completed a variety of pre-study questionnaires, including a 3-day voiding diary and voiding questionnaire, quality of life questionnaire for incontinence, incontinence impact questionnaire, Short Form McGill Pain Questionnaire, voiding and pain indexes (a subset of the interstitial cystitis symptom index and problem index), and an SF-36 Health Status Survey (a general quality of life questionnaire). Patients were older than 18 years with documented urgency, frequency and/or pelvic floor dysfunction resulting in a mean frequency of at least 10 voids per day and/or 3 per night (based on a 72-hour pre-intervention evaluation during the screening period). More conventional therapy, that is medical therapy, Kegel exercise, biofeedback and pelvic floor stimulators, had failed in all patients. Exclusion criteria included an active urinary tract infection, structural abnormality or urodynamically proved instability secondary to a known neurological condition, that is hyperreflexic neurogenic bladder.

After completing a variety of pre-study questionnaires, including incontinence impact, quality of life, voiding, void-

ing and pain, and 3-day voiding diary, patients gave a complete history and underwent physical examination, urodynamic studies and cystoscopy. Those patients meeting all requirements underwent 12 weekly neuromodulation sessions.

Peripheral afferent nerve stimulation was performed with the patients sitting in a frog-leg position with the soles of the feet touching and the knees flexed. The medial aspect of the lower extremities were palpated, and a sensitive pressure point was identified approximately 3 finger breadths cephalad from the medial malleolus (fig. 1). This point was about 1 finger breadth posterior from the edge of the tibia. A 34 gauge, solid stainless steel needle was advanced through the skin with the aid of an overlying plastic cylinder that was 3 mm. shorter than the needle. Once the skin was pierced the cylinder was removed, and the needle was advanced approximately 3 to 4 cm. posterior to the tibia and, if advanced further, would traverse anterior to the fibula. The needle trajectory was 60 degrees cephalad from a perpendicular line along the length of the tibia, advanced towards the patient head (fig. 2). Needles were placed bilaterally in a similar fashion.

An electrocardiogram ground pad was placed over the medial aspect of the calcaneus. A stimulator was then connected to the needle and the ipsilateral ground pad (fig. 3). Stimulation was titrated from 0 to 10 mA. with fixed pulse 200 microseconds at frequency 20 Hz. Proper needle placement was confirmed with great toe flexion and/or fanning or plantar toe flexion of ipsilateral digits 2 through 5. The stimulator was left with the patient controlling the power setting for 30 minutes. Therapeutic sessions were once a week for 12 weeks. If therapy was successful therapeutic treatments were titrated according to a patient specific protocol to determine the maximal interval of efficacy maintenance.

Statistical analyses were performed using Wilcoxon's signed rank test, and mean and median percentage changes. Analyses were performed using a priori specified dichotomous primary efficacy end point of a 25% decrease at week 12 relative to week 0 among patients with at least 10 voids per day at baseline. Because of the arbitrariness of the value 25% in defining mean target decrease, secondary analysis examined multiple cut points.

RESULTS

A total of 53 patients who met the entry requirements were enrolled in 1 of 5 sites listed in the table. Mean patient age was 57.4 years (range 24 to 80) and 90.2% of patients were female. A total of 47 patients (89%) completed the 12-week study. Two patients were excluded for noncompliance, 1 was started on anticoagulants (exclusion criteria) and 3 quit the study at 4, 5 and 6 weeks, respectively.

Our primary efficiency hypothesis was that at the end of 12 weeks greater than 50% of patients treated with the percutaneous device would have at least a 25% reduction in mean daytime voiding frequency. Figure 4 depicts mean voids per day by site, all patients and observations. Random coefficient regression analysis showed that all sites except 104 had statistically significant decreases from weeks 0 to 12. On average patients at site 104 had a decrease in mean daytime voiding frequency but the magnitude was smaller. Site 106

Percutaneous Sans study 01 in fall 1999

Site No.	Investigator	Institution	Total Pts.
101	Govier	Virginia Mason Medical Center	17
103	Litwiller	University of Texas, Southwestern Medical Center	10
102	Rosenblatt	Mount Auburn Hospital	8
104	Kreder	University of Iowa Hospitals, Clinics	10
106	Nitti	New York University Medical Center	8
Total investigational device exemption enrollment			53

[‡]UroSurge, Coralville, Iowa.



FIG. 1. Locate site with 3 finger breadths cephalad to medical malleolus.



FIG. 2. Place needle by having patient lie back with soles of feet together and knees abducted and flexed. Place guide tube over insertion site at 60 degree angle between ankle and foot. Gently tap needle to pierce skin.

appeared to have a somewhat greater decrease in mean daytime voiding frequency compared with the other investigational device exemption sites.

The site by slope interaction was quantitative, that is

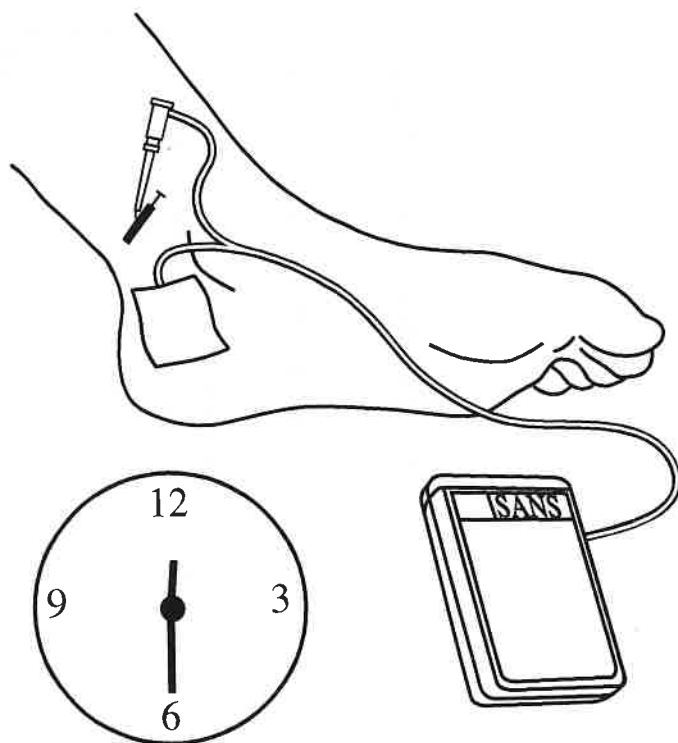


FIG. 3. Attach electrode and lead wire by placing electrode on same leg as needle near arch of foot. Connect grabber plug to needle on handle portion just above insertion point. Patient will control stimulation at comfortable level for 30 minutes.

effects were in the same direction, rather than qualitative, that is varying directions among sites, permitting the use of pooled summary measure of average efficiency. Dependent on baseline conditions, treatment with the percutaneous device in the acute treatment phase (12 weeks) resulted in at least a 25% reduction or improvement in daytime frequency for 55.2% of patients having 10 or greater voids per day ($p < 0.05$), an average 25% reduction or improvement in mean daytime voiding frequency ($p < 0.05$), an average 22% reduction or improvement in mean 24-hour voiding frequency ($p < 0.05$) and an average 70% reduction or improvement in excess, that is "mean daytime frequency defined as the mean number of voids greater than 10 per patient per day ($p < 0.05$)."

Figure 5 shows mean voids per night by all site observations. Random coefficient regression analysis led to the conclusions that there were statistically significant decreases in mean nighttime voiding from weeks 0 to 12, and mean decreases did not significantly vary among sites. Overall, treatment with the device resulted in an average 21% reduction or improvement in mean nighttime voiding frequency ($p < 0.05$).

Figure 6, A represents results from the incontinence impact questionnaire. Additionally, all data on all patients were used and again significant decreases were observed that did not significantly differ among sites. Overall, patients had a 35% reduction or improvement in daytime and nighttime urge incontinence or leak episodes during the 12-week treatment ($p < 0.05$). Figure 6, B depicts results for the pelvic pain intensity score by site. This analysis revealed a statistically significant decrease in mean pelvic pain intensity that did not vary significantly among sites. Overall, a 30% reduction or improvement in these select pain indexes were noted ($p < 0.05$). Figure 6, C shows results of the incontinence quality of life questionnaire. Additionally, a significant decrease was observed that did not differ among sites. Overall, a 20% improvement in these indexes were noted during the 12-week period ($p < 0.05$). Results relating to the 36 question

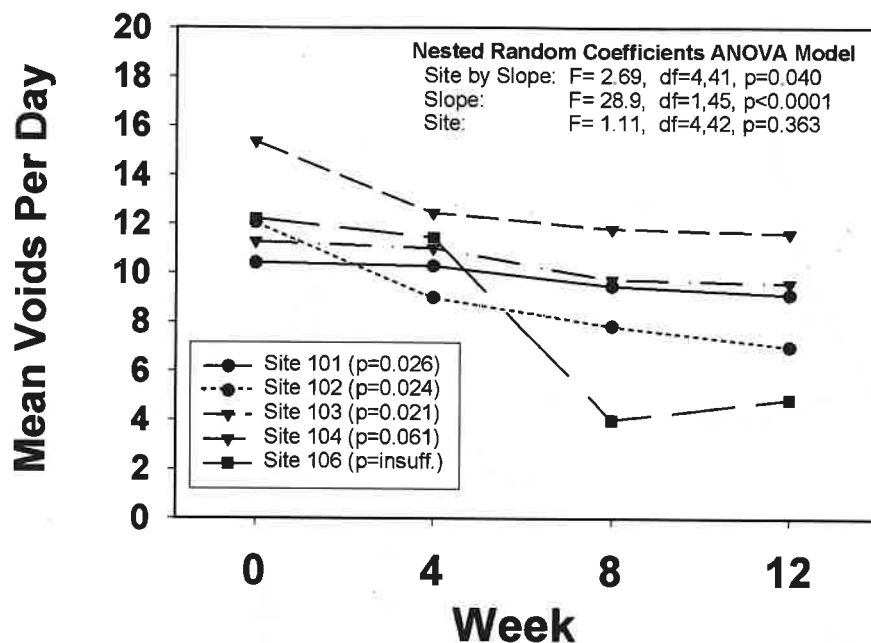


FIG. 4. Mean voids per day by site with all observations

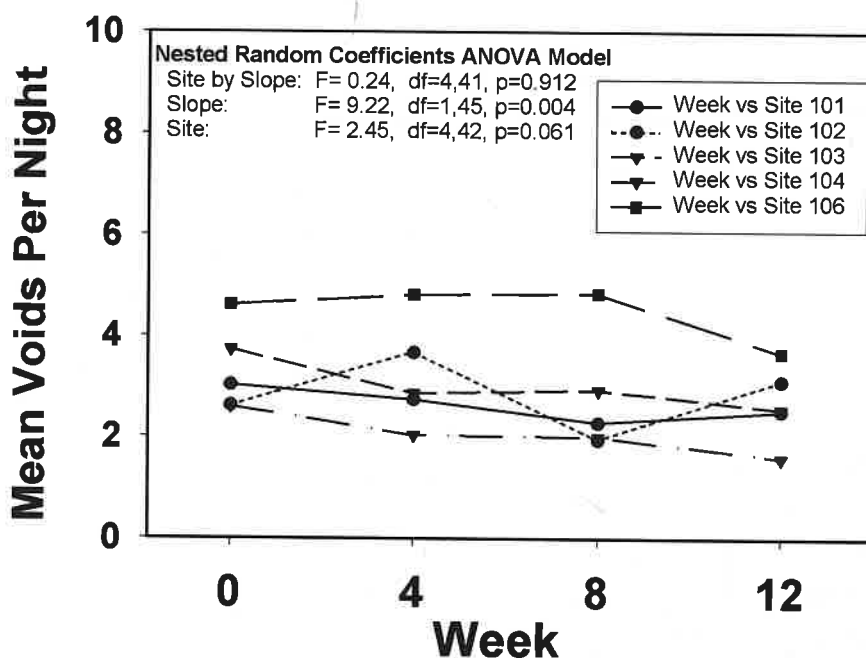


FIG. 5. Mean voids per night by site with all observations

social functioning score and the pelvic pain visual analog score are not represented. Improvements were noted in both of these areas but they were not statistically significant, and there was significant site variation in the pelvic pain visual analog score.

The presence of any major adverse events constituted the primary safety end point. Other events included were moderate to severe pain as determined by the validated pain assessment tool, infection caused by the procedure as detected by erythema or fever, and major device malfunction and/or failure. No serious or unanticipated adverse events were reported, and in no instances did an adverse event result in patient discontinuance from the study. One event, a cardiomyopathy, was classified as serious but it was believed not to be related whatsoever to the percutaneous procedure.

There were 3 events that met the definition of a primary safety end point adverse event, including moderate throbbing pain at the needle site in 1 patient, moderate right foot pain in 1 and stomach discomfort in 1. All events resolved spontaneously and did not impact or preclude further patient treatment. Of these 4 patients 2 continued in the tapering protocol.

Of the patients 71% were classified by the investigators as treatment successes after 12 weeks. Success was defined as patients who had at least a 25% reduction in daytime and/or nighttime frequency. These patients transferred into chronic treatment or tapering protocol. These treatments were customized to each individual patient, with the interval between treatment visits lengthened stepwise by intervals of 1 week until regression of efficiency was noted. Patients continued in this chronic treatment phase at investigator and patient

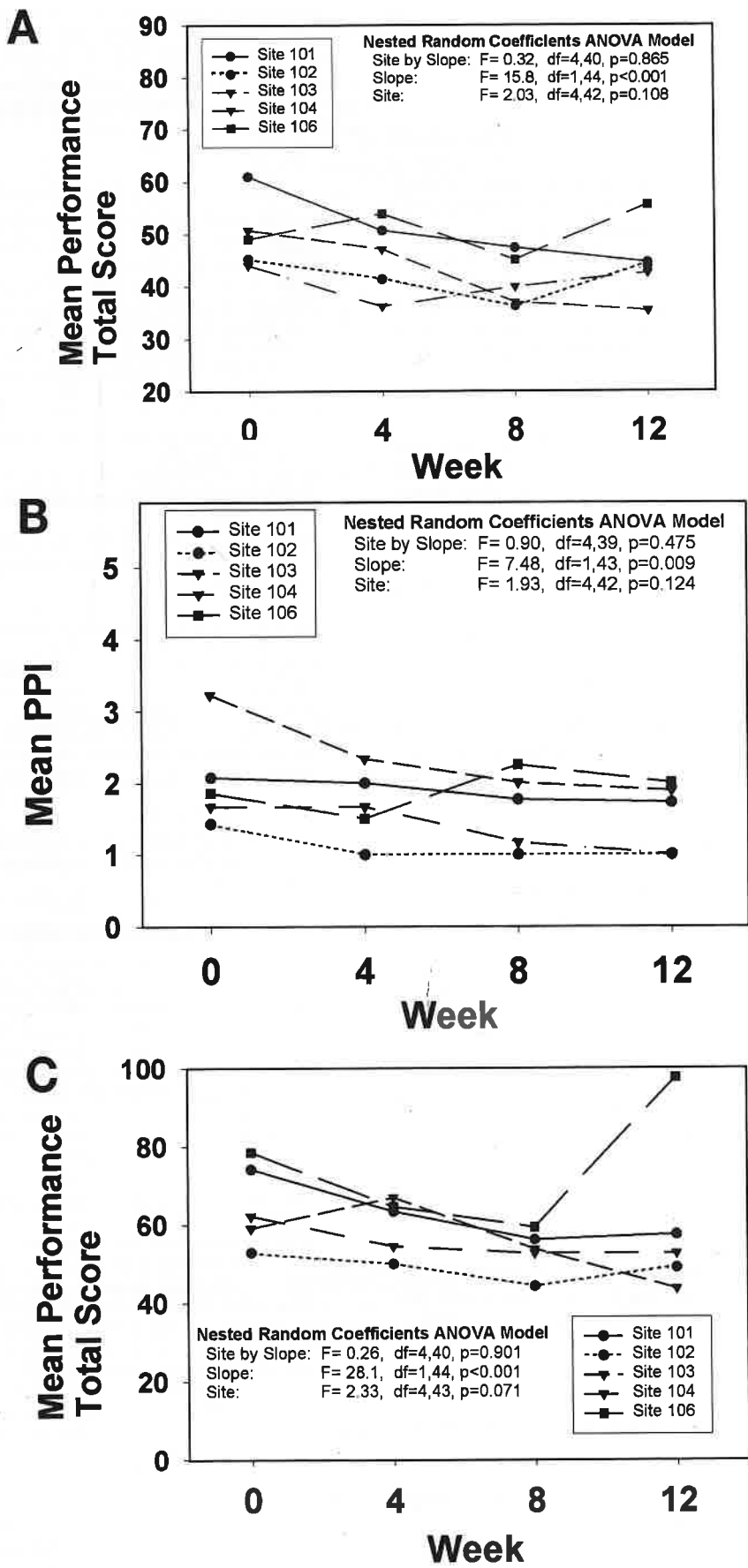


Fig. 6. All site observations of incontinence impact questionnaire (A), pelvic pain intensity (PPI) score (B) and incontinence quality of life questionnaire (C).

discretion or until Food and Drug Administration clearance. We did not have enough data to comment on mean treatment interval in this patient group.

DISCUSSION

Urologists frequently see patients with overactive bladders and pelvic floor dysfunction. These patients present with a multitude of symptoms, are labeled with a variety of diagnoses and have been subjected to a myriad of treatments, often to no avail. Unfortunately, overactive bladder and pelvic floor dysfunction are diagnoses of exclusion. We often cannot identify them on physical examination, see them through a cystoscope or identify them during urodynamic studies. The proximity of the structures and neuroanatomy leads to an overlapping of symptomatology in most individuals.

The elegant work of Tanagho and Schmidt demonstrated the complexity of these systems and the overlapping effects.⁶ In animal models and humans they reported that "detrusor activity is suppressed by sphincteric contractions. Thus, enhancing tone within the external sphincter will have a suppressive effect upon the detrusor and improve storage."

In a review article by Fall and Lindstrom it is noteworthy that afferent stimulation of anorectal branches of the pelvic nerve, dorsal penile nerve and clitoral nerve provides central inhibition of the preganglionic bladder motor neurons through a direct route in the sacral cord.¹ Recent work by de Groat showed the cortical neural control of voiding and how disruption of this control can lead to bladder overactivity and incontinence. He proposed damage to the central inhibitory pathways or sensitization of peripheral afferent terminals in the bladder unmasking primitive voiding reflexes that trigger bladder overactivity.¹⁰

To our knowledge until February 2000, the Interstim[®] PNE system device was the only Food and Drug Administration approved transcutaneous stimulator available. While the results are dramatic, with 47% of patients with end stage completely dry and 29% with greater than 50% improvement in incontinence after implantation, the procedure remains expensive, invasive and a third of the patients required surgical revision during the study.

The percutaneous afferent nerve stimulator offers patients and urologists alike a much safer, less invasive treatment alternative. An overall 25% reduction in daytime voiding frequency is impressive when one remembers that this is an average. Each of the centers had patients that did not respond as well as dramatic success stories, similar to the Interstim population. Another way to put these results into context is to look at the results of tolterodine in a much less affected group of patients. Appell found only a 20% reduction in overall frequency in a pooled series of 1,120 patients.¹¹

Urge incontinence was reduced by an average of 35% with the percutaneous device. When one remembers that approximately 50% of the patients undergoing test stimulations for the Interstim device were unsuccessful and, thus, not implanted, the percutaneous device results again become dramatic.

CONCLUSIONS

Our study confirms the safety and efficacy of afferent peripheral nerve stimulation for patients with refractive overactive bladders and pelvic floor dysfunction. In a multicenter prospective study we demonstrated statistically significant

§Medtronic, Inc., Minneapolis, Minnesota.

decreases in urge incontinence, and daytime and nighttime voiding frequency. Significant improvements were noted in select quality of life, social functioning and pelvic pain indexes. The technique is minimally invasive, requires 30 minutes per week and was associated with no significant adverse events or safety issues.

REFERENCES

1. Fall, M. and Lindstrom, S.: Electrical stimulation: a physiologic approach to the treatment of urinary incontinence. *Urol Clin North Am*, **18**: 393, 1991
2. Boyce, W. H., Lathem, J. E. and Hunt, L. D.: Research related to the development of an artificial electrical stimulator for the paralyzed human bladder. *J Urol*, **91**: 41, 1964
3. Bradley, W. E., Timm, G. W. and Chou, S. N.: A decade of experience with electronic stimulation of the micturition reflex. *Urol Int*, **26**: 233, 1971
4. Habib, H. N.: Experience and recent contributions in sacral nerve stimulation for voiding in both human and animal. *Br J Urol*, **39**: 73, 1967
5. Heine, J. P., Schmidt, R. A. and Tanagho, E. A.: Intraspinal sacral root stimulation for controlled micturition. *Invest Urol*, **15**: 78, 1977
6. Tanagho, E. A. and Schmidt, R. A.: Electrical stimulation in the clinical management of the neurogenic bladder. *J Urol*, **140**: 1331, 1988
7. Schmidt, R. A., Jonas, U., Oleson, K. A. et al: Sacral nerve stimulation for treatment of refractory urinary urge incontinence. *J Urol*, **162**: 352, 1999
8. McGuire, E. J., Shi-Chun, Z., Horwinski, E. R. et al: Treatment of motor and sensory detrusor instability by electrical stimulation. *J Urol*, **129**: 78, 1983
9. Stoller, M. L., Copeland, S., Millard, R. J. et al: The efficacy of acupuncture in reversing the unstable bladder in pig-tailed monkeys. *J Urol*, suppl., **137**: 104A, abstract 2, 1987
10. de Groat, W. C.: A neurologic basis for the overactive bladder. *Urology*, **50**: 36, 1997
11. Appell, R. A.: Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. *Urology*, **50**: 90, 1997

EDITORIAL COMMENT

This is a multicenter clinical trial study on percutaneous afferent neural modulation as a means of controlling urge incontinence and pelvic pain. The basic approach was to stimulate a peripheral nerve (tibial nerve) 3 fingers above the ankle for 12 weeks. A total of 53 patients were evaluated at 5 different sites. They did set a modest goal for themselves that at the end of treatment, 50% of the patients will have 25% improvement in symptoms. They evaluated their patients using incontinence impact questionnaires, as well as a pelvic pain intensity score and quality of life questionnaire. They reported 71% of the patients achieving success based on the criteria.

Their approach is relatively novel but not completely so as it has been reported before using the same principle of sacral root stimulation but instead of aiming at the sacral root itself, using 1 or another of its peripheral branches. As expected, it does give some response but much less than aiming at the sacral root itself. This technique is minimally invasive and can access neural circuitry controlling pelvic floor function as appreciated clinically with urge urinary incontinence and pelvic pain. These peripheral nerves may be less specific than if approached through percutaneous sacral nerve stimulation. Percutaneous afferent nerve stimulation and sacral nerve stimulation are not mutually exclusive modalities. Patients in whom afferent nerve stimulation fails may subcutaneously respond in a favorable fashion with sacral nerve stimulation.

Emil A. Tanagho
Department of Urology
University of California
San Francisco, California