Int Urogynecol J (2011) 22:407–412
DOI 10.1007/s00192-010-1235-9

ORIGINAL ARTICLE

Minimum 6-year outcomes for interstitial cystitis treated with sacral neuromodulation

Serge P. Marinkovic · Lisa M. Gillen · Christina M. Marinkovic

Received: 21 March 2010 / Accepted: 25 July 2010 / Published online: 17 September 2010

Abstract
Introduction and hypothesis Interstitial cystitis is a multifaceted medical condition consisting of pelvic pain, urgency, and frequency. Can sacral neuromodulation be successfully utilized for the medium term of ≥6 years in interstitial cystitis patients for whom standard drug therapies have failed?
Methods In our observational, retrospective, case-controlled review (January 2002–March 2004), we sought to discern whether neuromodulation could be successfully implemented with acceptable morbidity rates in interstitial cystitis patients. Thirty-four female patients underwent stage 1 and 2 InterStim placements under a general anesthetic. Simple means and medians were analyzed.
Results Mean pre-op/post-op pelvic pain and urgency/frequency scores were 21.61±8.6/9.22±6.6 ($p<0.01$), and mean pre-op/post-op visual analog pain scale (VAPS) were 6.5±2.9/2.4±1.1 ($p<0.01$). Median age was 41±14.8 years with a mean follow-up of 86±9.8 months.
Conclusions With a minimum 6-year follow-up we determined that sacral neuromodulation provides adequate improvement for the symptoms of recalcitrant interstitial cystitis.

We have not asked for nor received any funds from the federal, state, or local governments or universities.

We consign our rights to this paper to the International Urogynecology Journal and have not submitted this paper to any other journal.

S. P. Marinkovic (✉) · C. M. Marinkovic
Department of Urology and Urogynecology,
Women's and Children's Hospital,
Lafayette, LA 70508, USA
e-mail: urourogyn@yahoo.com
e-mail: serge1127@yahoo.com

L. M. Gillen
Department of Urology, Southern Illinois School of Medicine,
Springfield, IL 62521, USA

Keywords Sacral neuromodulation · Interstitial cystitis · 4 terminal tine leads

Introduction

Interstitial cystitis (IC) is a multifaceted medical condition consisting of a trilogy of symptoms, including pelvic pain, frequency, and urgency [1]. In some patients, this is primarily a disease of the bladder while in others it becomes a diffuse pelvic syndrome incorporating pelvic floor dysfunction [2]. The appearance of glomerulations and/or Hunner's ulcers (see Figs. 1 and 2) with cystoscopy and hydrodilation point the practitioner to a diagnosis of interstitial cystitis (Figs. 1 and 2) while painful bladder syndrome is identified by the same set of symptoms—pain, frequency, and urgency—without the cystoscopic evidence of bladder urothelial impairment [2]. With either disease, comorbidities are not uncommon and may include fibromyalgia, endometriosis, migraine headaches, irritable bowel syndrome, and Sjogren's disease. Not remarkably, social issues such as sexual, physical and verbal abuse, tend to be more prominent [3, 4]. A global synopsis indicates that Interstitial cystitis is a demanding disease often requiring multiple office visits and multi-specialty care for successful diagnosis and management [5].

Following diagnosis, some patients will respond to single or multimodal therapy [6], usually with a behavioral and/or pharmacologic (oral and/or intravesicular) therapeutic regimen; however, a subset of patients may not respond to this paradigmatic approach and will need another intervention [6–8]. In recent years, Neodynium:YAG laser therapy [9, 10], has been implemented for the coagulation of Hunner's ulcers. In more dire circumstances, trigone-preserving partial cystectomy with enterocystoplasty [11] has also been successfully utilized with good follow-up for end-stage

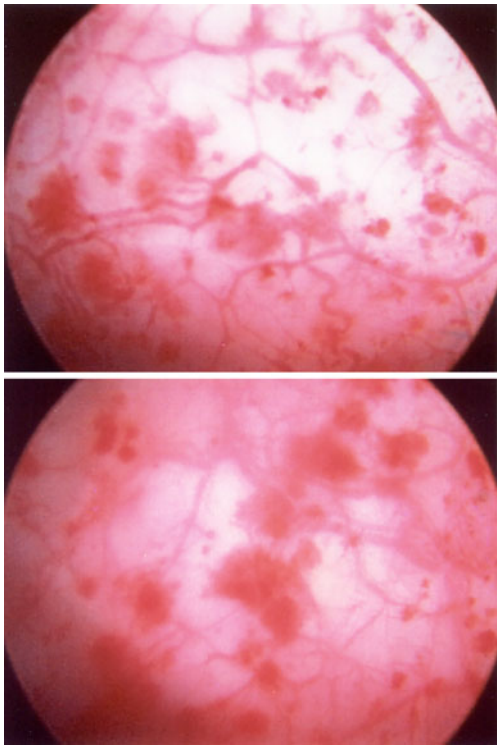

Fig. 1 Glomerulations appear after cystoscopy and hydrodilation

interstitial cystitis. Newer methods of neuromodulation (i.e., ischial–rectal–pudendal approach) have been studied as alternatives but only with short-term evaluation (less than 1 year follow-up) and have not gained substantial utilization in the United States or Europe [12]. Direct stimulation of the transforaminal sacral afferent roots with an implantable lead and implantable pulse generator neuromodulating device (IPG, InterStim, Medtronic, Minneapolis, MN, USA) has received ample attention and was approved by the Food and Drug Administration for intractable overactive bladder symptoms and nonobstructive urinary retention in 1997 and 1999, respectively [13]. Because of the overlap in symptom similarity between overactive bladder symptoms and interstitial cystitis, studies have been performed to elucidate the potential role of sacral neuromodulation in the treatment of this chronic pain syndrome [2, 13, 14]. As of 2010/2011, sacral neuromodulation has not been approved for the treatment of interstitial cystitis; however, studies incorporating the technology demonstrate a significant therapeutic application with reproducible symptom relief. Unfortunately, these studies have a short-term follow-up of 1 year or less or evaluate patients with painful bladder syndrome [2, 12–15].

Material and methods

Our evaluation was an observational, retrospective, case-controlled study of 34 consecutive patients with cystoscopic-confirmed interstitial cystitis. Patients experienced recalcitrant symptoms that remained unimproved with conventional behavioral and medicinal therapy. All consented to undergo sacral neuromodulation (InterStim, Medtronic Inc., Minneapolis, MN, USA, IPG model #3023 and tined lead with larger lead #1 model #3093) stage one and two* under a general anesthetic between January 2002 and March 2004 for improvement in their frequency and urgency. The study received an internal review board approval. All patients were informed about the Medtronic-recommended precautions against the utilization of magnetic resonance imaging, as the lead and implantable pulse generator could be affected. Workup included a complete history and physical examination, urine analysis with microscopic evaluation and culture, videourodynamics with

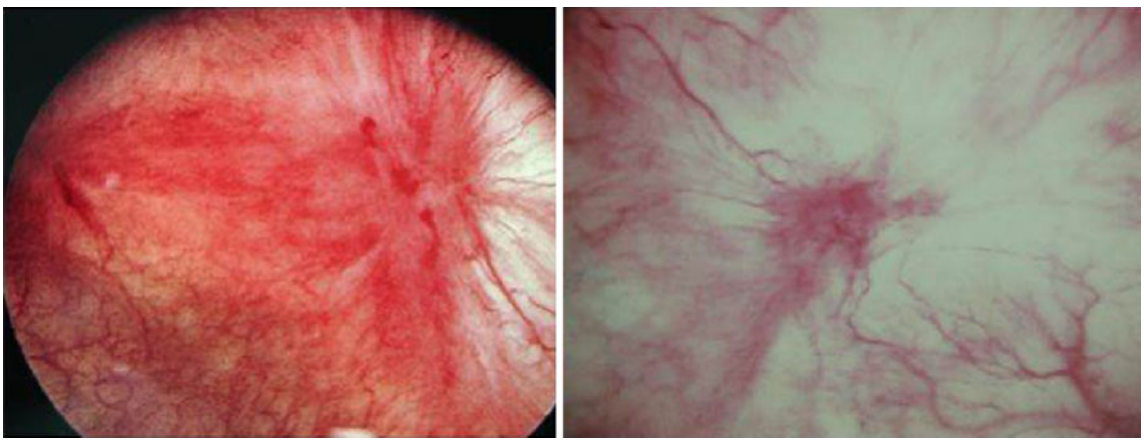

Fig. 2 A Hunner's ulcer is an epithelial injury into the submucosa of the bladder wall. Bleeding may occur and can easily be made quiescent with either a Yag or Holmium laser ablation. The pictured Hunner's ulcer is in the process of healing. 254×190 mm (72×72 DPI)

EMG, office cystoscopy, pre-operative voiding diary, and post-operative 72-hour micturition log, hydrodilation as well as technical data on implantation and operative revisions. In addition, patients received serial pelvic pain and urgency/frequency (PUF) scores.** All patients had attempted maximal conservative therapies including pentosan polysulfate sodium [16], amitriptyline [17], imipramine [18], gabapentin [19], hydroxyzine [20], and intravesical dimethyl sulfoxide [21] before undergoing staged sacral neuromodulation. Videourodynamics testing was not performed post-operatively to detect differences in voiding parameters, as the procedure's invasiveness and the concomitant exposure to radiation energy may have proven detrimental. Failure was defined as the recurrence of urgency/frequency (or <50% improvement in the number of voids). In the event of failure, patients did not progress from stage 1 to stage 2 implantable pulse generator placement. Responses to pelvic pain improvement questions were recorded; however, this was not an inclusionary criterion for stage 2 implantation. Lead displacement was not considered a failure if revisional surgery returned the patient to a 50% improvement/reduction in symptoms. Battery replacement was also not considered a therapy revision or failure if due to battery quiescence. Statistical analysis was performed using the Statistical Package for Social Sciences, version 11.0 (SPSS, Chicago, IL). Analysis included simple means, medians, and standard deviations (Tables 1, 2). Comparisons of pre-operative and post-operative voided urine volumes were performed with an analysis of covariance (ANCOVA).

*Only those with a >50% reduction in frequency and urgency were candidates for stage 2 implantation.

**Serial PUF scores were used instead of UDI-6 and IIQ7 scores because the latter two are primarily utilized for stress incontinence while the PUF score is designed to be specific for interstitial cystitis screening and symptom improvement with treatment.

Description of sacral neuromodulation procedure under general anesthetic

The patient was brought into the operating room table and intubated. A general anesthetic was used, but no paralytic agents were utilized so as not to interfere with intra-operative neurological testing. The patient was turned and placed into the prone position. The lower back, buttock, rectum, and perineum were prepped with betadine soap and paint, then toweled dry. The patient was also grounded. The buttocks were taped to the metal of the operating room table to better expose the anus for the bellows associated with neurological S_3 testing. Sterile conventional draping followed. The patient did not receive a bowel preparation but did receive broad-spectrum antibiotics to cover staph, strep, and pseudomonas. The portable fluoroscopy was placed to outline the poster-oanterior (PA) view of the sacrum and pelvis, first from a PA view then from a lateral confirmational view. The sacral spinous processes from S_1 through S_5 were outlined on the back with ink (horizontal line), then both sciatic notches were outlined with ink for a vertical line that crossed the spinous processes at S_3. The PA view was utilized to place the introductory needle into S_3 foramen and the lateral view to check for correct foraminal placement and depth. Once placed, we tested the needle by applying a low current while

Table 1 Patient demographics and results

Category	Result	Range
Median age (years)	41±14.8	23–61
Mean body mass index	26.71±6.88	21.5–37.2
Duration of IC (years)	7.81±5.58	1–20
Mean follow-up (months)	86±9.8	60–94
Pre-operative VAP	6.51±2.9	2–10
Post-operative VAP[a]	2.43±1.1*	0–6
Mean pre-operative PUF score	21.67±8.6	11–36
Mean post-op PUF score[a]	9.22±6.6*	02–17
Re-operative rate (%)	27	
Mean pre-operative 24 hour number of voids (*n*)	17.87±7.3	10–28
Mean post-operative 24 hour number of voids[a] (*n*, $p<0.01$)	8.1±5.3	5–16
Mean pre-operatively voided volume (ml)	141.±51.8	10–227
Mean post-operatively voided volume[a] (ml, $p<0.01$)	251±96.8	80–372
Mean pre-operative nocturia (number of voids)	4.1±2.2	1–8
Mean post-operative nocturia[a] (number of voids, $p<0.01$)	1.4±0.96	0–6
Patient satisfaction (%, n=24/30)	80	

*$p<0.01$

[a] Pearson coefficient derived from statistical comparison between pre-operative and post-operative values

Table 2 Comparison of pertinent study parameters in Marinkovic's and Comiter's utilization of sacral neuromodulation to treat interstitial cystitis

	Marinkovic, SP	Comiter, CV
Number of patients	30	25
Age (years)	41±14.8	47
Median follow-up (months)	86±9.8	14
Pre-op average number of voids	17.87±7.3	16.9±4.6
Post-op average number of voids	8.1±5.3	8.4±3.5
Mean pre-op PUF score's	21.67±8.6	Not available
Mean post-op PUF score's	9.22±6.6	Not available
Pre-op visual analog pain scale	6.5±2.9	5.8±2.2
Post-op visual analog pain scale	2.4±1.1	1.6±1.5
Pre-op nocturia (voids per night)	4.1±2.2	4.5±2.7
Post-op nocturia (voids per night)	1.44±0.96	1.68±1.07
Pre-op mean voided volume (ml)	141±51.8	111±45
Post-op mean voided volume (ml)	277±96.8	264±102

moving the needle in and out of the S_3 foramen. Bellows stimulation (contraction of the levator ani) and ipsilateral plantar flexion of the big toe are needed for confirmatory S_3 placement. Placement in S_4 leads to bellows only while S_2 placement leads to ipsilateral calf rotation. With constant maneuvering of the needle to obtain a strong bellows and plantar flexion, we placed, via Seldinger technique, a guide wire through the needle core and removed the needle to make the incision larger with a scalpel. A white introducer was placed over the guide wire next and the guide wire removed. The tine lead was then advanced under lateral radiological guidance and stimulation of all four leads recorded to see which leads gave the strongest bellows/plantar flexion with the least amount of power. Then with a push-and-pull technique, the introducer was removed utilizing fluoroscopy without moving the position of the four terminal leads (0–3). The end of the lead was brought out to a same-sided 5-cm buttock pocket that was fashioned below the belt line and above the buttock line to avoid the sensation of sitting on the IPG. With stage 1, the IPG placed is the larger belt-held model versus the totally implantable pulse generator. The latter implantable unit is reserved for those who have successfully passed their testing period with a better than 50% reduction in symptoms. The skin can be closed via any manner (i.e., staples or suture closure). The Federal Drug Administration-approved criteria for sacral neuromodulation placement includes the following: recalcitrant overactive bladder symtoms of frequency, urgency, and nocturia which have not responded to at least two anticholinergic medications either secondarily to side effects or lack of efficacy (at least a 50% reduction in frequency, urgency). Following sacral neuromodulation placement, we expect patients to achieve at least a 50% reduction in frequency and urgency episodes while increasing their average voiding volume.

Results

Thirty of 34 patients completed testing (see Table 1). Four patients did not proceed from stage 1 to stage 2 implantation secondary to less than a 50% improvement in symptoms. The median age was 41±14.8 years and the median follow-up was 86±9.8 months (see Table 2 for all study parameters). Mean pre-op PUF [22, 23] scores were 21.67±8.6. After a minimum 72-month follow-up, mean post-op PUF was 9.22±6.6 ($p<0.01$). Mean pre-op/post-op VAPS were 6.5/2.4 ($p<0.01$). The recommended time frame of up to 1 month for abatement of pain may not be long enough to fairly assess improvement of this symptom. More indicative during this time may be the amelioration of urgency and frequency. There were five cases of lead migration (secondary to falls and automobile trauma) and three implantable pulse generator erosions (secondary to trauma) without infection for a re-operation rate of 27% (eight out of 30). While this rate may seem high, included in the study was a group of relatively young, physically active patients. The complications were due to accidents (e.g., kick to the side of the right buttocks during a martial arts bout, fall off a 15-foot ladder, fall through a porch floor, car door slammed against the buttock during a tornado alert).

Discussion

For women who have failed conservative interstitial cystitis and perhaps painful bladder syndrome treatment paradigms, including biofeedback, oral medication, and intravesical therapy but still harbor recalcitrant symptoms, there are other successful alternative therapies. Comiter [13] prospectively evaluated 25 patients with interstitial cystitis defined by the strict National Institute of Arthritis, Diabetes

and Digestive and Kidney disease criteria that had failed conservative therapy. Comiter utilized two different study cohorts. Study cohort 1 patients underwent percutaneous test stimulation and, later, those deemed successful (>50% reduction in urgency and frequency) underwent complete lead and implantable pulse generator placement. In 2001, the Food and Drug Administration approved the now conventional-staged approach, which incorporates placement of the tined lead and a temporary adjustable pulse generator over a certain duration of testing (1–4 weeks). With a greater than or equal to 50% improvement in voiding parameters with reduced urgency and frequency, the patient can be offered to proceed to a stage 2 implant which entails the placement of a much smaller pulse generator either under a general, regional, or local anesthetic. Interestingly, none of Comiter's study patients evaluated with hydrodistension demonstrated Hunner's ulcers (our study n=8/30 or 27%), but all had evidence of glomerulations. Seventeen of the 25 patients (68%) underwent complete sacral neuromodulation placement, 13 of 15 (87%) under the staged cohort completed a stage 2 implantation while only four of ten (40%) with the percutaneous evaluation achieved complete implantation. We have not utilized the percutaneous approach for assessment in favor of the staged approach. All patients experienced an efficacious improvement in multiple voiding and pelvic pain parameters as reflected by the statistically significant reduction in both PUF and VAPS scores. We contrast our study's similar results with a 72-month minimum review to Comiter's mean 14-month follow-up. Mean age for both studies were similarly young women; our women's median age was 41±14.8 years contrasted to Comiter's mean age of 47 years. Our mean follow-up was 86±9.8 months compared to Comiter's 14 months. Average number of voids (bold face is our study result compared to Comiter's) per 24 h±SD were 17.87±7.3/16.9±4.6 improving to 8.1±5.3/8.4±3.5 both p<0.01 (Table 2). Nocturia improvement was also statistically significant for both investigators 4.1±2.2/4.5±2.7 and improved in both groups to 1.44±0.90/1.68±1.07 voids at nighttime (p<0.01). Mean voiding amounts pre/post-operative were 141±51.8/111±45 ml to 277±96.8/264±102 ml, p<0.001. For overall symptom improvement, we utilized the pain, urgency, and frequency scores [22, 23] and did not incorporate the Interstitial Cystitis Symptom Index or the Interstitial Cystitis Problem Index as in Comiter's study. Mean pre-op/post-op PUF scores were 21.61±8.6/9.22±6.6 (p<0.01) (Table 2). Visual analog pain scale pre/post-operative was also analogous between these two studies 6.5±2.9/5.8±2.2 to 2.4±1.1/1.6±1.5 (p<0.01). There were five cases of lead migration, three implantable pulse generator erosions secondary to trauma without infection for a re-operation rate of 27% (eight out of 30). With this comparison, we may determine that sacral neuromodulation is both therapeutic in the short-term (mean 14 months) and medium term (mean 6–7 years) with good outcomes, most importantly in the PUF scores. The limiting factor for comparison is that Comiter's study predates the initiation of PUF scores in the literature while ours initiates almost at the outset with Parsons and associates' [22] October 2002 publication.

Recently, Powell and associates [2] retrospectively re-evaluated their sacral neuromodulation patients' treatment results with a marginally different disease entity, painful bladder syndrome. With this condition, there is no demonstration of glomerulations or Hunner's ulcers with cystoscopy and hydrodilation. Because both Comiter and Marinkovic studies precisely define their patient populations as women with interstitial cystitis, comparison with Powell and associates may not be appropriate or useful.

Conclusion

Encouraging assessments following the use of sacral neuromodulation, including appreciable patient satisfaction scores and diminution in symptom severity as tabulated by PUF scores, may encourage our specialty to entertain more valid, evidence-based studies (fulfilling level 1b or 2) to confirm our results and pursue the approval of sacral neuromodulation for the treatment of interstitial cystitis.

Conflicts of interest None.

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