



Sacral neuromodulation for chronic pain conditions

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Chronic nonmalignant pain syndromes of the pelvis or genitourinary are well described in both the gynecology and urology literature, though the origin and physiology of the pain syndromes are not well understood. Patients frequently have multisystem complaints including voiding dysfunction, chronic pelvic pain, and genitourinary hypersensitivity. Both the patient's history and physical examination can be a powerful diagnostic tool in unmasking a chronic pain disorder. However, laboratory and imaging studies often are unrevealing, with no physical cause for the pain disorder being identified. This can lead to frustration and depression in these patients, which may lead them to develop complex psychologic adaptive and maladaptive methods of coping with their pain as it affects their lives. Although there are numerous pain syndromes involving the pelvis or sacrum and urogenital tract, syndromes that have had good pain control outcomes with sacral neuromodulation are interstitial cystitis (IC), prostatic dysuria or epididymo-orchalgia, vulvodynia, and coccydynia.

Interstitial cystitis is a chronic debilitating condition of the urinary bladder characterized by symptoms of dyspareunia, irritative urinary symptoms, and nocturia. The epidemiology of the disorder is not well established, but there are an estimated 700,000 cases of IC in the United States. It occurs primarily in women. Onset is predominately in adulthood, although IC does occur in childhood. The median age of onset is 40 years; however, there is a bimodal distribution with one peak in the twenties and a later one in the fifties. In general, patients suffer with the symptoms for 3 to 7 years before the correct diagnosis is made [1]. Numerous

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pathophysiologic mechanisms have been proposed, but none have been proven. Bladder wall defects, auto-immune disorder, viral or bacterial infection, toxin exposure, pelvic floor dysfunction, and inflammatory response are possible causes [2]. An animal model, the naturally occurring disease in cats, may help to provide insight into the bladder response to injury. The feline interstitial cystitis follows a similar chronic waxing and waning time course as interstitial cystitis in humans [3]. The diagnosis is made clinically and by cystoscopy with hydrodistention and sometimes biopsy when other pathologies have been excluded. In symptomatic patients, glomerulations on bladder distension are indicative but not pathognomonic for nonulcerative interstitial cystitis [4]. Patients with IC will often have characteristic findings on cystoscopic examination including small petechial hemorrhages called glomerulations, although the classic Hunter's ulcer is seen in only about 10% of patients. Histologic examination of bladder biopsies from patients with long-standing interstitial cystitis reveal marked edema and injury to blood vessels and nerves within the muscularis layer, which are all consistent with the pathologic findings of neurogenic inflammation [5]. The traditional nonsurgical management of interstitial cystitis includes dietary changes, antihistamines, tricyclic antidepressants, oral and intravesicle glucosaminoglycans, hydrodistention, pain management, and emotional support.

Prostodynia is defined as persistent complaints of urinary urgency, dysuria, poor urinary flow, and genital or perineal pain. The new classification of prostatitis syndromes by the National Institutes of Health clearly defines the diagnostic criteria for categorization according to the clinical symptoms. National Institutes of Health (NIH) consensus classification identifies chronic prostatitis or chronic pelvic pain syndrome (CP/CPPS) based on the presence or absence of leukocytes in expressed prostatic secretions (EPS), postprostatic massage urine (VB3), or seminal fluid analysis. In the United States, approximately 25% of men presenting with genitourinary tract problems are diagnosed with "prostatitis", and prostodynia accounts for approximately 30% of those cases [6]. Up to 65% of patients with chronic prostatitis have the nonbacterial form. The disorder is seen in 5 of every 10,000 outpatient visits by men. On physical examination, the prostate is typically normal with no sign of tenderness on palpation. The diagnosis of prostodynia is one of exclusion. It has been suggested that prostodynia may be a male variant of interstitial cystitis and in fact represent different manifestations of the same disease process [7].

In 1983, vulvodynia was first recognized as a diagnosis in the medical literature [8]. Vulvodynia is defined as chronic vulvar discomfort, characterized by the patient's complaint of vulvar burning, itching, and dyspareunia [9]. Greater than 50% of the time all therapeutic interventions tried by patients made the vulvar symptoms no better or worse. Although the true incidence of this disorder is unknown, reports have shown that as many as 15% of patients seen in a general gynecologic practice meet the criteria for this diagnosis. Currently there remains no universally established classification, assessment, and treatment for vulvodynia.. Like most pelvic pain syndromes, the physical examination is often unremarkable. However, histologic studies of vulvar biopsies show a chronic inflammatory

reaction of the mucosa along with neural hyperplasia [10]. These findings are similar to those seen in IC and are also consistent with neurogenic inflammation. There is a serious need for greater understanding of this disorder as the evidence suggests that, although not life-threatening, vulvodynia seems to have a significant impact on quality of life.

Coccydynia is defined as pain or discomfort in and around the coccyx, typically worsened when sitting and especially with rising from the sitting position. Apart from those patients with local trauma the cause of this pain disorder is not known. Rarely lesions have been identified including hemangioma [11], intradural schwannoma [12], intra-osseous lipoma [13], although most cases are idiopathic. This pain disorder can be significantly debilitating for patients and should be readily treated aggressively.

Traditional medical and surgical therapies

Standard medical treatments include the use of NSAIDS, muscle relaxants, tricyclic antidepressants (amitriptyline), anti-epileptics (gabapentin), and opioids. Trials of amitriptyline and gabapentin are particularly important as these syndromes display symptoms characteristic of neuropathic pain. Medications unique to the treatment regimen of interstitial cystitis include oral treatment with pentosan polysulfate (Elmiron), amitriptyline, or hydroxyzine, and intravesical treatments with heparinlike medications, dimethyl sulfoxide, or BCG [14]. Anti-histamines also have been used, based on the premise that local release of histamine by mast cells contributes to the pathogenesis of IC. The use of antihistamines has shown some promise [15,16]. Elmiron, a synthetic polysaccharide, works by correcting defects in the epithelial permeability barrier of the bladder. It has shown modest benefits [17] and is part of the standard medical treatment for IC.

More invasive therapies for interstitial cystitis include hydrodistention or bladder instillations. While hydrodistentions are typically performed as part of the diagnostic work-up for IC, they also provide some symptomatic relief. Results from this treatment are variable and only temporarily effective [18]. In addition, the procedure often results in an eventual worsening of the patient's symptoms. Bladder instillations, another mainstay in the treatment of IC, use various agents such as dimethyl sulfoxide (DMSO), silver nitrate, heparin, and bacillus Calmette–Guerin (BCG). These instillations may provide temporary symptomatic relief, but again frequently lead to an eventual worsening of the pain. The caustic nature of some of these agents is likely damaging to the bladder mucosa and its innervation [19]. Hence, the short-term benefits may be in part caused by a chemical neurolysis. While distention and instillation may provide temporary relief, they are likely further damaging the bladder and its nerve supply by mechanical and chemical tissue injury.

Radical surgical therapy for IC has been considered a treatment of last resort when the therapies, mentioned earlier, have failed. The options include transurethral resection of Hunter's ulcers, cystectomy and urinary diversion, and cystec-

tomy with enterocystoplasty. Even cystectomy fails to abolish the pain in up to 50% of patients [20]. Many patients with enteroplasties will develop interstitial cystitis-like changes in their reconstructed bladders [21].

Therapies for NIH category III chronic nonbacterial prostatitis or chronic pelvic pain syndrome (CPPS) commonly include antibiotics (notably tetracyclines, quinolones, and macrolides), anti-inflammatory agents, and alpha blockers. Newer approaches include trials of finasteride, quercetin, and rofecoxib [22]. More invasive ablative techniques such as transurethral microwave hyperthermia [23] and transurethral needle ablation [24] may be a possible treatment option for patients with chronic nonbacterial prostatitis that is unresponsive to conservative therapies.

Treatment for vulvodynia requires the identification of possible dermatological factors including candidiasis, atopy, dermatographism, and irritant contact dermatitis. Identification of these factors and directed management can lead to symptomatic improvement in patients [25]. When no specific pathologic causes can be identified treatment options may include calcium citrate, tricyclic antidepressants, topical corticosteroids, topical nitroglycerin [26], and physical therapy with biofeedback. Other treatment modalities can include surface electromyography-assisted pelvic floor muscle rehabilitation [27] or perineoplasty for women who do not achieve satisfactory relief of vulvodynia or dyspareunia with nonoperative treatments [28]. Several treatment modalities for coccydynia have been used; these include rubber ring cushions, sacrococcygeal rhizotomy [29], physiotherapy, manipulation [30], local or epidural injections, and coccygectomy [31]. Most patients respond (60%) to local or epidural injection with corticosteroids and local anesthesia, whereas those patients with severe refractory coccydynia occasionally require coccygectomy. Ninety percent of those individuals that received coccygectomy had pain relief [32]. Neuromodulative techniques versus destructive lesions has been trialed for this unique pain disorder.

Neurophysiology of pelvic pain disorders

Pelvic pain syndromes appear to be neuropathic in nature, displaying characteristics of hyperpathia and allodynia. In the case of IC, low volume filling of the bladder is painful and non-painful intravesical contents such as potassium cause discomfort [33]. In addition, tissue biopsies in patients with vulvodynia [34] and interstitial cystitis [35] reveal changes consistent with neurogenic inflammation. A common cause of bladder dysfunction in women is neural damage following hysterectomy. Of note, up to 40% of women with interstitial cystitis have undergone recent hysterectomy before the onset of symptoms [36]. This scenario, in which injury or transient inflammation results in chronic pain and vasomotor changes within the bladder, is reminiscent of reflex sympathetic dystrophy (RSD) or complex regional pain syndrome type I (CRPS I) seen in the extremities. The concept that interstitial cystitis and other pelvic pain disorders may represent RSD has been previously suggested [37]. The variable clinical presentations may represent stages in continuity of CRPS I of the pelvis.

Most of the traditional therapies mentioned earlier are destructive lesions aimed at the nerve supply to the pelvis. The presumption that these disorders represent neuropathic pain conditions should lead to the development of techniques similar to those applied for other neuropathic disorders. When treating neuropathic pain, ablative techniques can often fail to permanently resolve the pain disorder. Changes in primary afferents lead to plasticity in second order neurons within the central nervous system (CNS). Subsequent ablation of the peripheral neural pathway is unsuccessful for chronic pain conditions because the abnormal focus of neural activity has been shifted into the central nervous system. Therefore, neuromodulatory procedures may be more appropriate treatments for these pelvic pain syndromes.

Neuromodulation for chronic painful conditions of the pelvis

Neuromodulation of the sacral nerves is not an entirely new concept. The first sacral nerve stimulators implanted in 1981 by Tanagho and Schmidt [38] were performed for the indications of urinary urge incontinence, urgency-frequency, and nonobstructive urinary retention. Since that time, observations have been made for benefits beyond voiding disorders. These additional benefits have included re-establishment of pelvic floor muscle awareness, resolution of pelvic floor muscle tension and pain, decrease in vestibulitis and vulvadynia, decrease in bladder pain (interstitial cystitis), and normalization of bowel function. Believing that the pain in these conditions was neuropathic, the authors first began treating these syndromes at their institution (University of Tennessee, Memphis) in 1998. All patients referred to the authors had failed the traditional therapies and were told that radical surgical intervention cystectomy was their only alternative. The authors' initial attempts to manage these patients were with intrathecal drug pumps [39]. Five of six intrathecal trials were successful and four patients eventually underwent permanent implant. All patients required a mixture of at least two drugs. Of note, clonidine was the common drug used in all implanted pumps. Only two of these patients continue to use their infusion pumps. Given the inherent complications associated with intrathecal drug delivery and the logistics associated with frequent pump refills the authors elected to try alternative therapies.

Based on its success in treating other presentations of complex regional pain syndrome, spinal cord stimulation (SCS) would seem to be a good therapeutic modality to treat these conditions. However, several technical factors significantly limit its application to the treatment of pelvic pain. First, the dorsal cerebrospinal fluid layer at the level of the conus is quite thick, significantly insulating the spinal cord from the epidural electrodes. Secondly, the conus is relatively mobile and it is difficult to maintain consistent paresthesias when stimulating this region. Lastly, there are few large fiber afferents from the pelvis and thus stimulation at this level frequently produces paresthesias in adjacent or undesirable regions. With the knowledge of pelvic innervation a novel approach to sacral nerve stimulation through both percutaneous and surgically implanted paddle leads were investigated.

Pelvic neuro-anatomy

The pelvis is innervated by a complex network of peripheral sympathetic, parasympathetic, and somatic nerve structures. Projections from both the thoracolumbar and sacral segments of the spinal cord convey these fibers, which converge into peripheral neuronal plexuses. The pelvic viscera are parasympathetically innervated by way of S2–4 and sympathetically innervated T12–L2. Most of the sympathetic outflow to the pelvic viscera arises in thoracolumbar spinal cord segments and is conveyed through the superior hypogastric plexus. The parasympathetic outflow is by way of S2–4 roots that converge into the preganglionic pelvic splanchnic nerves. Lastly, the somatic efferent and afferent innervation to the pelvis originates from sacral spinal cord levels S2–S4. Nerve branches originating from the S3 sacral level primarily supply the anterior perineal musculature. Thus the S3 roots are the typical targets for neurostimulation procedures aimed at treating pelvic floor dysfunction. However, sensations from the pelvic floor are mainly conveyed by way of the sacral afferent parasympathetic system (S2–S4), with a far lesser afferent supply from afferents traveling with the thoracolumbar sympathetics. Therefore, neurostimulatory procedures aimed at treating pelvic pain syndromes should include the S2, S3, and S4 roots.

Sacral neuromodulation techniques and case reports

With the advent of techniques to perform retrograde nerve root stimulation [40], selective stimulation of the S2, S3, and S4 nerve roots became possible. Retrograde techniques were used to implant four quadripolar leads. The optimal array consists of two lateral leads following the course of the S2 roots up to the point where they enter their respective foramen and two medial leads overlying the S3 and S4 roots along their caudal course. This procedure has a steep learning curve and the authors' early attempts were complicated by wet taps and intrathecal electrode implantations. These complications occur most frequently during insertions at the L5–S1 interspace because of the posterior angulation of the sacrum. Therefore, the authors elect to enter at the L2–3, L3–L4, or L4–L5 level whenever possible. In some cases (epidural fibrosis, spina bifida occulta [41], and the rest) it has not proven technically feasible to implant percutaneous leads. In those instances the authors have elected to perform an open procedure, placing bilateral paddle leads. This is easily performed through a small incision and laminotomies on the inferior margin of L5 and the superior margin of the sacrum. Leads are then inserted bilaterally in a retrograde fashion beneath the dorsal aspect of the sacrum.

Case #1 interstitial cystitis (percutaneous lead-retrograde method)

This 77-year-old woman had been diagnosed 14 years ago with biopsy proven interstitial cystitis. Numerous medical therapies including bilateral hypogastric plexus blocks yielded no pain relief. Using a caudal approach, bilateral dual Quatrodos (Advanced Neuromodulation Systems (ANS) Allen, TX) were placed



Fig. 1. Interstitial cystitis (percutaneous lead-retrograde method).

overlying the S2, S3 and S4 nerve roots. The patient reported excellent paresthesia coverage, pain relief, and marked improvement in bladder function. Following a 3-day trial of stimulation she proceeded to receive a permanent device (Fig. 1).

Case #2 interstitial cystitis (paddle lead)

A 30-year-old woman seen initially in June 1998 with diagnosis of IC since age 23 believed that she had a lifelong history of urgency and frequency, but was told that it was something normal. Prior treatments were oral medication (Elmiron, tricyclic medications, opiates, and cell membrane stabilizers); repeated hydro-distensions, and multiple courses of intravesicular instillations of DMSO. In August 1998, attempted insertion of percutaneous SNR stimulator lead, met with great difficulty, ultimately had wet tap; for this reason the lead was removed and an incision was made over L5S1. After complete spinal anesthetic was obtained two lamitrode 44 paddles were placed in the sacrum such that they overlay at S2, S3, and S4 roots. In October 1998, she presented with increased IC pain; on further discussion the authors determined that she had been out of town the previous week and had not followed her typical IC diet. She stated she had begun to feel so well that she had gotten a little lax on monitoring her diet. She is the mother of a 1-year-old boy. (She did not use her stimulator during pregnancy) (Fig. 2).

Using the techniques mentioned earlier the authors have successfully treated over 40 patients with interstitial cystitis and other pelvic pain syndromes. The authors' initial results [10] are quite promising with an average reduction in visual analog pain scores (VAS) of 55% (mean pre-op VAS 9.1, mean post-op VAS 4.0). In addition, approximately one-third of patients were able to discontinue their opiate medications and one-third were able to significantly reduce their opiate requirements. The procedure also seems to be effective in treating the patients'



Fig. 2. Interstitial cystitis (paddle lead).

voiding dysfunctions. Fifty percent of patients reported reduced frequency and 25% had measured increase in bladder capacities. The main complications of the procedure are infection, subdural implant, and CSF leak, with an overall complication rate of approximately 5%. Similar results have been seen with a large prospective clinical study, demonstrating that sacral neuromodulation is 94% effective treatment for dysfunctional voiding and pelvic pain in patients with interstitial cystitis [42].

Stimulation parameters and programming are somewhat different than that used for SCS. Amplitudes employed are typically lower and the therapeutic window (painful threshold or perceptual threshold) is narrower. Multiple cathodes are frequently used. Frequency rates are variable, but high frequency stimulation (>900 Hz) is often required for bouts of refractory pain. Over 90% of the authors' patients have required a period of high frequency stimulation. Because of this, it is the authors' preference to use radiofrequency coupled systems to provide greater flexibility without concern for battery life.

Case #3 epididymo-orchalgia

A 44-year-old man presented with history of epididymitis and prostatitis for approximately 6 years. He was referred to the senior author for possible neuromodulation therapy. Numerous pain medication including opioids, tricyclic antidepressants, and Neurotin provided minimal pain relief. A trial of L1–L2 stimulator and an S2–4 stimulator with dual percutaneous octrodes lead through the sacral hiatus was initiated. The patient returned with an approximately 75% pain relief with the neuromodulation and proceeded with permanent implantation (Fig. 3).

The most common technique used is percutaneous placement of leads by way of the dorsal sacral foramen using unilateral or bilateral S3 electrodes. Recent studies have explored this technique to treat pelvic pain [43,44]. The results show modest

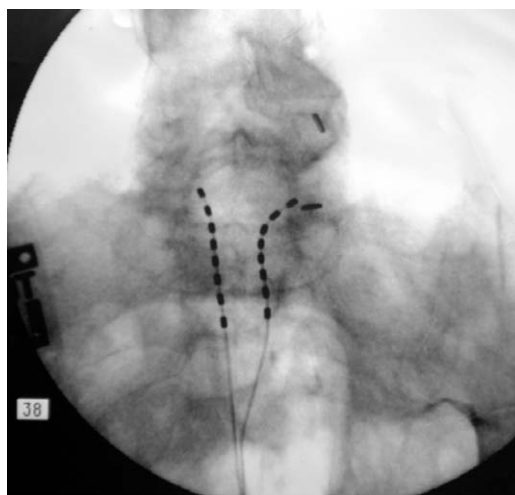


Fig. 3. Epididymo-orchalgia.

benefit with 60% to 70% of patients experiencing at least 50% improvement in their pain. However complication rates were as high as 18%. A major problem with this technique is lead migration. One study [45] documented an average lead migration of 12 mm. In the multicenter study for urge incontinence, 39% of patients required either electrode revision or system explanation. The tangential placement (as opposed to retrograde along the course of the roots) of leads with this technique makes the problem of lead migration even more troublesome as fewer contacts are in proximity to the root. In addition, targeting only the S3 roots may be inadequate if the goal is to treat pelvic pain and not just voiding dysfunction.

Case #4 vulvodynia

A 71-year-old woman with 9-year history of vulvodynia had undergone three laparoscopic procedures without improvement in her pain. Numerous medications, counseling, and biofeedback had been unsuccessful in reducing her discomfort. Because of significant lumbar stenosis and spondylolisthesis a trial of sacral root stimulation was performed through the sacral hiatus. Excellent paraesthesias was achieved throughout the perineum and peri-rectal region. The patient had excellent pain relief and returned for permanent implantation.

Summary

Some of the pelvic pain syndromes seem to have features of neurogenic inflammation and neuropathic pain in common. As opposed to being separate disease entities, they may represent a spectrum of clinical presentations of CRPS I of the pelvis. Sacral nerve root stimulation provides good symptomatic relief of pain and voiding dysfunction. The techniques of retrograde root stimulation may

offer superior results with fewer complications and lead migrations when compared with other methods. Perhaps neuromodulation should be used earlier in the treatment paradigm for these disorders, before the potentially injurious procedures of hydrodistention, bladder installations, and cystectomies.

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