**Prospective Review** 

# Role of Lumbosacral Retrograde Neuromodulation in the Treatment of Painful Disorders

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**Background:** Neuromodulation is an effective and reversible treatment option for chronic intractable pain. Spinal cord stimulation (SCS) represents a field of application of neuromodulation and is known to be effective for several conditions including complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS), and chronic leg and back pain. SCS has some technical limitations that can be bypassed through retrograde neuromodulation.

**Objective:** To examine the safety and efficacy of retrograde neuromodulation in consecutive patients with neuropathic pain in the perineum or lower limb.

**Study Design:** Prospective chart review analyzing one year of retrograde stimulation in our department.

**Methods:** We present a series of 10 patients who underwent retrograde neuromodulation at the University General Hospital of Valencia (Spain). We analyzed the variables that can improve the outcome and help physicians choose retrograde neuromodulation.

**Results:** Seven of 10 patients had an effective treatment and 3 patients had an ineffective stimulation. In the group with the effective treatment the most represented type of pain was radiculopathy and perineal pain.

**Limitations:** This is a prospective, single-center study with a relatively small number of patients and no control group.

**Conclusion:** Retrograde neuromodulation seems to be effective in patients that present with a well localized pain with a clear dermatome distribution. We found retrograde neuromodulation to be effective in radiculopathy related to FBSS. We found it to be limited in the treatment of perineal pain probably due to technical limitations and anatomical reasons besides the lack of knowledge of the etiology of this pain model and the exact mechanisms of action of neuromodulation.

**Key words:** Chronic pain, spinal cord stimulation, retrograde neuromodulation, sacral root stimulation, perineal pain

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ince its introduction in 1967 by Shealy et al (1), spinal cord stimulation (SCS) has been applied in different clinical indications and pain syndromes. Although the introduction of SCS was inspired by the gate theory, postulated by Melzack and

Wall in 1965, its exact mechanisms of action are still largely unknown. According to Oakley and Praguer (2), the effects of SCS are mediated by a complex set of interactions at several levels of the nervous system. Linderoth and Meyerson (3) published that segmental spinal mechanisms like inhibition of neuronal activity in the dorsal horn of the spinal cord and activation of descending pain-controlling pathways may relate to the pain relieving effect of SCS. However, there is evidence that the SCS effect is mediated also by the activation of a spinal-brainstem-spinal loop. Animal models (4,5) suggest an effect by attenuating dorsal horn wide dynamic range (WDR) or "convergent" neuronal hyperactivity. Neurochemically, SCS may act to restore normal GABA levels in the dorsal horn, and possibly to effect the release of adenosine. There is reason to assume that the descending noradrenergic system takes part as well.

The conventional approach for electro stimulation catheter placement within the epidural space has historically been performed in a cranial direction with catheter insertion over the spinal cord. Normally, the needle is placed inferior to the interlaminar space, advanced cranial and parallel to the angle of the lamina (6,7). However, this approach does not allow access to individual nerve roots in the foot, low back, buttock, or perineum because of the opposing caudal anatomic position of the respective nerve roots in the lumbar and sacral plexus (7,8).

In addition, the need to stimulate exactly a specific area to obtain a selective and localized analgesic effect while avoiding the discomfort derived from a generalized stimulation and paresthesia perception, not overlapping the area of pain, make the stimulation of the dorsal columns of the spinal cord a non optimal technique (6).

For these reasons, between the late 90s and the beginning of the new century, new techniques to reach the epidural space have been developed in order to facilitate the approach to these difficult anatomic regions (7,9-17). Percutaneous cephalocaudal implantation of selective nerve root stimulation electrodes over sacral nerve roots may offer superior results with fewer complications and lead migrations when compared with other methods. This approach allows reaching some peripheral regions of the spinal canal achieving good paresthesia coverage and pain relief even when the conventional approach fails to obtain a good result.

Although early reports of the use of retrograde stimulation were done more than 10 years ago, the number of papers published among all the publications of neuromodulation is really limited. One possible reason is that heterogeneous indications make it difficult to publish a long series on a particular indication.

Therefore, we wanted to publish a retrospec-

tive study of a year's work in our pain department on the performance of this specific neuromodulation technique.

# METHODS

In order to better understand the role of retrograde neuromodulation, we analyzed the patient population of the Pain Department of the University General Hospital of Valencia (Spain) to identify patients implanted with a retrograde electrode during one year.

The retrograde approach was performed percutaneously. With the patient in prone position, an introducer needle was placed in the lumbar interlaminar space but in the opposite direction compared to a classic epidural approach. The epidural space was approached through the L2-L3, L3-L4, and L4-L5 interlaminar space (8,10,12,17) using the "loss of resistance" technique. When the epidural space was localized, the electrode was inserted through the needle and directed, using real time fluoroscopic vision, toward the lumbar caudal, lumbar transforaminal, or sacral space, according to the neural target (Figs. 1-2). The specific material used was the 1x4 Pisces Compact lead model 3887 for selective radicular stimulation and 1x8 Compact Percutaneous Lead Model 3778 for midline lumbosacral retrograde stimulation (Medtronic, Minneapolis, USA). When the electrode reached the exact neural target and the patient experienced good paresthesia coverage, the needle was withdrawn and the electrode was fixed and connected to a temporary pulse generator for the trial period (6,8).

During the period of analysis, 10 patients were included in the retrograde neuromodulation protocol. The mean age was 53.6, ranging from 28 to 78. The male/female ratio was 5/5.

Before a patient's inclusion in the neurostimulation protocol, no satisfactory pain relief was achieved both with conservative treatments and with other interventional treatments.

We decided to conduct retrograde stimulation directly, considering that the evidence accumulated in the literature was superior compared to conventional SCS. Kapural et al (18) published a case series of patients with chronic intractable visceral pelvic pain with adequate pain relief using conventional SCS. They stated, based on a previous paper published on the treatment of cancer patients (19), a possible mechanism for the pain relief was the modulation of the midline dorsal column visceral pathway. Also based on pure anatomical facts, they stated that the conus at T12-L1 is an ideal location for stimulation because a lead placed there





could capture the maximal amount of innervation to the pelvis and thus minimize the amount of nociceptive input that could escape through alternate pathways. Nevertheless in this paper clearly visceral nociceptive pain was the taxonomy presented in all patients, in comparison to our series which was neuropathic pain.

All patients were tested with a temporary neurostimulator, and only after a positive trial period, was the definitive system implanted. Seven of 10 patients had a positive trial, reporting more than 50% pain relief as well as about 60% improvement in the activities of daily living, and subsequently underwent the intervention to implant the definitive internal pulsed generator (IPG).

The average age in the group of patients with effectiveness neuromodulation was 50.6, ranging from 28 to 78. Five patients were men and 3 women. All patients reported a persistent pain relief in the target area of neuromodulation. In one patient the system was removed after 3 months because of a repeated local infection of the lumbar wound and subcutaneous pocket not controlled by antibiotic therapy. Diagnosis, pain topography, and approach utilized to place the electrode in the group with effective treatment are reported in Table 1.

# RESULTS

Three of 10 patients reported pain relief less than 50% and a lack of improvement in the activities of

daily living during the trial period and therefore the definitive system wasn't implanted and the electrode was withdrawn. In all 3 patients the pain was localized in the perineal area. This fact was also raised in a previous paper published by Hunter et al (20) on chronic pelvic pain, which remains complex and often resistant to neuromodulation. These authors considered using the sacral region as a target. The main reason for poor results was the lack of consensus on the optimal location for lead placement.

With one patient who suffered from vulvodynia we used a transforaminal approach, with one patient who suffered from interstitial cystitis we used a lumbar caudal approach, and with the last patient with a diagnosis of peripheral neuralgia we used both a lumbar caudal and transforaminal approach.

Diagnosis, pain topography, and approach used to place the electrode in the group with an ineffective treatment are reported in Table 2.

# Discussion

Although SCS is a widely used technique for pain treatment, the correct selection of patients is still a cause of debate. As chronic pain patients are affected on an individual basis by neurophysiological, emotional, and behavioral influences that govern their perception of pain and of pain relief, making the determination of suitability for implantation should be based on a

	Sex	Age	Pain Taxonomy	Pain localization	Approach
# 1	М	49	Perineal neuralgia – Coccygodynia	Coccyx and heels in the S1 region	Lumbar caudal
# 2	М	37	Stump limb pain	Front of the stump, trigger point in the dorsal internal area of the leg	Lumbar caudal – Transforaminal
# 3	F	28	Interstitial cystitis	Perianal area	Lumbar caudal
#4	М	59	L5 radiculopathy – Neural entrapment	Postero-lateral area of the left leg	Lumbar caudal
# 5	М	61	Sciatic popliteal extern nerve lesion	Lateral leg face up to foot toes	Lumbar caudal
# 6	М	42	FBSS	Lumbar zone, left leg irradiation in typical sciatic topography	Lumbar caudal
# 7	F	79	L5-S1 radiculopathy	Typical sciatic topography	Lumbar caudal

Table 1. Patient features - Diagnosis, pain topography and approach. Group with effective treatment.

 Table 2. Patient features – Diagnosis, pain topography and approach. Group with ineffective treatment.

	Sex	Age	Pain Taxonomy	Pain localization	Approach
# 8	F	33	S2, S3, and S4 sacral nerve roots peripheral neuropathy	Vulvar labia irradiated to the anal area and to the internal thigh	Lumbar caudal
# 9	F	76	S3, S4, and S5 sacral nerve roots peripheral neuropathy	Vaginal and anal pain	Lumbar caudal
# 10	F	74	S1, S2,0 and S3 sacral nerve roots peripheral neuropathy	Sacral and perineal area	Lumbar caudal Transforaminal

thorough analysis, both medical and behavioral (21). Indications for SCS range from neuropathic pain to ischemic pain including other conditions such as chronic lower urinary tract symptoms and colorectal disorder (6,8,22,23).

Different reviews have been done in the past in order to assess the efficacy of SCS in patients with failed back surgery syndrome (FBSS), chronic back and leg pain (CBLP) (24), and complex regional pain syndrome (CRPS) (25,26). Randomized controlled trials (RCTs) of SCS have been undertaken for FBSS, showing evidence of the benefit of SCS over comparative therapy. However, a recent systematic review of the benefits of SCS for the treatment of CRPS and FBSS emphasizes the need for more methodologically rigorous studies to provide definitive data regarding improvement in pain and function in the short- and long-term (27).

Particular pain areas remain difficult to stimulate with SCS, including the low back, buttocks, feet, groin, pelvis, and neck (28). Furthermore, some pathways such as those supplying the S2-5 dermatomes, are located somatotopically deep within the spinal cord, and tend to be out of reach from SCS. Percutaneous retrograde neuromodulation is an alternative technique that allows bypassing this obstacle when selective nerve root stimulation (SNRS) for the treatment of intractable pelvic pain is necessary (9-12).

The stimulation of dorsal columns or dorsal roots depends on several variables; one of these variables is the distance between the electrode itself and the neural structure to stimulate. In this sense, the thickness of the cerebrospinal fluid (CSF) in the lumbar and sacral region can act as an insulating barrier between the electrodes and neural structures; therefore, lumbosacral CSF volume is a variable according to vertebral levels (29,30), affecting the distance between the electrode and the neural target, making it necessary to augment the stimulation parameters to obtain adequate paresthesia (8).

Retrograde neuromodulation allows placement of the electrode closer to the neural structure to obtain better paresthesia in a selected dermatome area and avoid patient discomfort.

While anterograde SCS and retrograde SCS allow stimulation of the dorsal columns of the medulla, the retrograde root stimulation allows direct stimulation of a selective single or multiple spinal roots (lumbar or sacral) in order to obtain pain relief in a localized anatomic area.

This approach bypasses the conus medullaris and

the pelvic afferent fibers. Stimulation at this level is complex, often resulting in ineffective paresthesia or paresthesia in unwanted regions (31). In addition pelvic pain is mediated mainly by fibers of the S2-S4 roots (31-33); therefore, intercepting the sacral root through the sacral foramen allows matching the electrode and neural structures in a more stable area (31). Unfortunately, in this area there are limited places for tissue anchorage, and this represents a technical disadvantage that can lead to migration of the electrode. Moreover in this study (31) the authors report a high complication rate related to this technique.

The main indication for retrograde stimulation is in patients with failed conventional SCS or patients who are not candidates for conventional SCS because their painful area is inaccessible to SCS, according the anatomical and neurophysiological correlation of stimulation of the intraspinal structures (7,9-13,34-38) (Table 3).

All patients treated in our pain department and included in the percutaneous cephalocaudal implantation of selective nerve root stimulation electrodes complied with the above-mentioned indications.

We performed 7 retrograde approaches with positive outcomes, 4 for radicular pain, one for interstitial cystitis, one for coggygodynia, and one for stump limb pain.

In the group with the effective treatment, the most represented category of patients is that with radicular pain/plexopathies with 5 cases representing 71.4%, followed by one patient with perineal pain/interstitial cystitis and one patient with coccygodynia representing the remaining 28.6%.

According the literature, sacral neuromodulation is known to be an effective therapy for urological and colorectal functional disorders such as urinary voiding disorders, fecal incontinence, and constipation, and for the treatment of pelvic pain related to interstitial cystitis and anorectal pain disorder (7,9-13,34,39).

Other conditions that can benefit from sacral neuromodulation are lumbosacral radiculopathies, disco-

Table 3. Indications for percutaneous retrograde neuromodulation					
Perineal pain, that includes vulvodynia, prostatodynia, pudendal neuralgia, obturator neuralgia and sexual dysfunction					
Coccygodynia					
Pain related to interstitial cystitis or colorectal pain					
FBSS, plexopathies					
Urologic and colorectal functional disorders					

genic back pain, coccygodynia, pudendal neuropathy, and vulvodynia (7,16).

Pelvic pain syndrome is a condition characterized by neuropathic pain with hyperpathia and allodynia similar to CRPS affecting the extremities (31). The syndromes compromise the quality of life of the patient and are very difficult to treat with conventional therapy (31).

Interestingly in our series we found that all patients with failed neuromodulation were affected by pelvic pain, although with different etiology. One patient had a diagnosis of vulvodynia, one of interstitial cystitis, and one of non-specific peripheral neuropathy. The reasons for failure of sacral neuromodulation in these 3 patients can be related to different causes. Although sacral neuromodulation allows reaching the sacral neural structure in a relatively easy way, the technique has some technical limitations. First, the CSF layer in the conus is quite thick and can insulate the target structure from the electrodes; second, the neural structure at this level is relatively mobile and can cause difficulty in maintaining the electrode perfectly coupled with its target; third, stimulating the pelvic area can produce paresthesia in an undesirable region provoking patient discomfort (33).

In addition, a complex network of peripheral nervous structures innervates the pelvis. The S3 root is the typical target for neurostimulation procedures but the S2 and S4 roots can also be a target for neuromodulation in pelvic pain syndromes (32,33).

Furthermore the etiology of pelvic pain is still unclear. Pelvic pain is defined as non-malignant pain perceived in structures related to the pelvis. Pain can be associated with symptoms of lower urinary tract, sexual, bowel, or gynecologic dysfunction (40). A hypothesis is that pelvic disorders represent a spectrum of clinical separation of CPRS type I of the pelvis (33).

Conversely with respect to the evidence of the effectiveness of SCS in the treatment of CRPS type I, we had only one case of pain relief in patients suffering from pelvic pain.

Sacral neuromodulation seems to be effective for the treatment of pelvic pain and voiding dysfunction in patients with interstitial cystitis refractory to conventional therapy (32,39).

Usually patients with interstitial cystitis had a history of many years of uncontrollable pain and of ineffective therapy such as hydro distension, bladder instillation, and cystectomies.

Feler et al (33), in a paper published in 2003, reviewed the role of sacral neuromodulation in the

treatment of chronic pain and suggested that the ineffective therapeutic attempt in this patient could lead to bladder injury worsening the initial pathology and therefore stated that sacral neuromodulation should be used before these potentially injurious procedures provoke further damages. This theory could explain the failure of retrograde neuromodulation in our patient that was referred to our pain service after a very long time (36 months) of ineffective treatments.

One patient in our series had a diagnosis of vulvodynia. Vulvodynia is defined as a vulvar discomfort, often described as a burning pain, without relevant clinical findings or specific identifiable neurological disorders (41). This kind of pain affects the quality of life, limiting social interaction (41). In our patient no satisfactory pain relief was achieved during the trial period and thus the transforaminal electrode was removed. Interestingly, the patient currently reports a good pain control with transcutaneous electric nerve stimulation (TENS). Although in a single case, the difference in outcome between these 2 apparently similar techniques once again emphasizes the lack of knowledge about the exact mechanisms of action of neuromodulation and about the exact features of chronic intractable perineal pain.

It is important to emphasize the role of different medical specialists in the diagnosis and prognosis of these pathologies. Usually it is the urologist, gastroenterologists, gynecologist, or even the general practitioner who performs the primary diagnosis. From that perspective, the therapeutic approach is confined to the boundaries of knowledge in their specialty, i.e. unidisciplinary standardized treatment. Unfortunately, some patients are refractory to standard treatments. Multidisciplinary evaluation and treatment of patients must start as early as possible and should include urologists, gynecologists, gastroenterologists, psychologists, and anesthesiologists.

The last patient with failed retrograde neuromodulation suffered from sacral and perineal pain. The patient didn't find satisfactory pain relief with either the transforaminal or lumbar caudal approach. Subsequently the patient reported good pain relief with an injection of botulin toxin on the right pyramidal muscle. The response from botulinum toxin could indicate an error in the diagnostic process with the sacral and pelvic pain representing only an irradiation of myofascial pain. Another possible hypothesis is that the myofascial pain treated with botulinum injection was coexisting with sacroiliac joint pain and that the relief of only one of 2 pains provided the patient satisfactory pain relief. Sacroiliac joint pain is generally difficult to diagnose and difficult to treat. The difficulty in treatment is in part due to the complexity of its innervation that consists in an anterior and posterior innervation from different spinal metameric levels from L2 to S3 (34).

In our case the retrograde neuromodulation didn't provide enough improvement in sacroiliac joint pain control, but a recent work by Kim and Moon (42) demonstrates that intractable sacroiliac joint pain can take advantage of retrograde sacral nerve stimulation. A possible explanation of retrograde neuromodulation failure in our patient is incorrect electrode placement due to the complexity of sacroiliac joint innervation. In addition sacroiliac pain is usually considered a nociceptive pain that doesn't respond to neuromodulation therapy. More studies are required in order to establish the role of retrograde neuromodulation in sacroiliac joint pain. Even this case highlights the need of more exhaustive research about the mechanisms of action of neuromodulation along with an understanding of the etiology of pain syndromes that can benefit from neuromodulation such as intractable pelvic pain and intractable sacroiliac joint pain.

The final consideration concerns the psychological assessment of patients for neuromodulation. As the literature suggests (43) a psychological assessment of patients before implantation of a neuromodulation device is nowadays mandatory. Especially considering chronic pain, the multifactorial experience including behavioral, emotional, and cognitive contributions have to be considered. In our hospital we habitually perform a psychological evaluation of patients before neuromodulation therapy. This kind of comprehensive evaluation is necessary because psychological assessment is one variable predicting implant success (43).

Interestingly, even though eligible for the technique, all the patients in the group with ineffective therapy presented with an alteration in the psychological profile defined as depression, anxiousness, and anorexia. Conversely, in the group with effective treatment, only 2 patients presented with a similar alteration in their psychological profile.

Looking at the different patients included in this study, it is difficult to propose a single protocol for the selection of patients for neurostimulation. Specifically patients with chronic pelvic pain have not just a physical health condition but a problem with significant emotional, social, sexual, physical, and psychiatric implications. For this reason, the accurate collection of a thorough medical history should be prioritized, and it's important that patients completely understand the path of the therapy, the true potential benefits, and the possible technical difficulties (43). The role of the multidisciplinary treatment team, we believe, is fundamental in the management of patients with chronic pain. However, this relationship is not without difficulties, as patient adherence to therapeutic protocol and the professionals responsible for their treatment protocols, not only depends on the patient, but also on their social and family environment. This, together with the different etiologies of pain in this group of patients, could explain the failure of these 3 cases of retrograde neuromodulation therapy.

To reinforce this need of more exhaustive knowledge, a recent paper by De Ridder et al (44) presented a new modulation modality that offers potentially better pain relief than conventional SCS and that causes paresthesia in only a minimum part of the patient treated. This new finding forces pain specialists to reconsider the role of paresthesia in SCS, one of the most important parameters considered in electrode placement, and to re-evaluate their awareness of the neuromodulation technique. Furthermore the possibility of obtaining satisfactory pain relief without triggering paresthesia opens the way to perform new more accurate studies that are necessary to increase our knowledge about this pain control technique. Also, Snellings and Grill (45), using an animal model, very recently quantified electrical stimulation settings in sacral nerve roots, with possible future implications in the clinical neuromodulation of pelvic pain disorders.

### CONCLUSION

Conscious of the limited population of our study, we do not intend to offer a complete coverage of neuromodulation knowledge, but to offer a real vision of retrograde neuromodulation in the management of chronic intractable neuropathic pain. These results seem to suggest that retrograde neuromodulation can potentially be indicated as a therapeutic option in those patients with well-localized pain with clear dermatomal distribution in pelvic area.

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