

Case Report

RETROGRADE EJACULATION FOLLOWING LUMBOPELVIC SYMPATHETIC NEUROLYSIS – A CASE SERIES

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Background: Sympathetic neurolysis, or sympathectomy, is an established modality for the treatment of chronic pain. In cases of chronic pelvic pain (CPP), the ganglion of impar (GI) and the superior hypogastric plexus (SHP) are widely accepted targets for such therapy.

Objective: While diagnostic injections typically predate any neurolysis for the purpose of ascertaining any potential efficacy for interrupting a particular pathway, careful attention is equally paid to evaluate for possible adverse events - in the case of lumbopelvic neurolysis, retrograde ejaculation (RE) is one such possibility.

Study Design: A case series.

Setting: An outpatient pain management clinic.

Methods: We present 3 male patients with CPP treated who underwent neurolytic procedures targeting the GI and SHP.

Results: The first patient developed RE after undergoing a simultaneous neurolysis of both the SHP and GI, in the same sitting. The second and third patients both experienced temporary RE immediately after diagnostic blockades of the SHP, following GI neurolysis that was performed several weeks prior.

Limitations: Cause-effect conclusions cannot be drawn from the results of a case series.

Conclusions: RE is a potential consequence of combined or serial SHP and GI neurolysis. While neurolysis of either the GI or SHP individually have not been known to cause RE in men, this case series demonstrates the potential risk in causing it when both structures are simultaneously incapacitated in some form; as such, the authors recommend against both structures being ablated or disabled concurrently without careful evaluation with temporary blockades first. In an effort to avoid such a complication or evaluate for the possibility in a particular individual, we recommend that an individual with CPP, who has already been treated with a neurolysis, undergoes diagnostic blocks first on whichever of the 2 structures has not yet been ablated to carefully evaluate if RE will occur.

Key words: Retrograde ejaculation, superior hypogastric plexus, ganglion impar; neurolysis, chronic pelvic pain, male infertility, diagnostic block

Neurolysis is an established therapy for the treatment of certain types of chronic pain with an acceptable risk-benefit ratio (1). Neurolysis includes a

variety of different procedures (i.e., radiofrequency ablation, cryoablation, chemical neurolysis, etc.) (2) with the central premise of destroying a pain transmitting nerve, or at the very least limiting its ability to transmit pain, all the while preserving vital surrounding structures. Perhaps the greatest utility of neurolysis is in cases where surgical treatment is not the preferred curative method or there is simply nothing that can be outright “corrected” (e.g., Complex Regional Pain Syndrome or CRPS) (3). Regardless of the exact premise, neurolysis can serve to decrease a patient’s pain simply by destroying its pathway to the cognitive centers in the brain.

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As it relates to chronic pelvic pain (CPP), rarely is there an obvious defect or detectable abnormality one can point to as the pain generator that can be fixed procedurally. In cases of pudendal entrapment (4), endometriosis (5), pelvic congestion syndrome (6), and the like, there is a relatively obvious pathophysiology one can potentially rectify and potentially repair. In other cases, when the cause or source of discomfort is not readily apparent, neurolysis may be the more acceptable treatment option as it is dependent on the route of the pain signals and not the cause or source.

The key to a successful neurolysis is the identification of the key conduits or neural pathways through which the pain signals are traveling (7). This is typically accomplished through the use of diagnostic injections (8) whereby a physician will inject a sodium channel blocker, such as lidocaine or bupivacaine, on a nerve, group of nerves, ganglion, plexus, etc. If the pain is improved during the time the target is under the influence of the injectate, it stands to reason that the target may be in part responsible for transmitting pain. In the case of CPP, pain pathways are often rooted in the sympathetic nervous system (9,10) – in particular the ganglion of impar (GI) and the superior hypogastric plexus (SHP).

Neurolysis of the GI and SHP was first described by Plancarte in 1990 (11) as a means of treating pelvic pain secondary to cancer. These have since been adapted for the treatment of non-malignant pain due to their efficacy and low potential for complication (9,10,12). While the GI and SHP are accepted targets for neurolysis, certain male patients may potentially be at risk for RE. We present a case series of 3 men with CPP who experience RE after blockade/neurolysis of the SHP, following a GI several **days prior**. {AU: In the abstract, it says several weeks prior. Was it days or weeks?}

Retrograde Ejaculation

Male infertility accounts for roughly 20% of all infertilities among couples of reproductive age (13–15). Although the prevalence of RE has been estimated 0.3-3.2% of all male infertility (16–19), the true prevalence may be higher due to under-reporting from the fear of social stigmatization (20). It has been shown

that infertile men who desire fatherhood are at a higher risk to experience low self-esteem, depression, anxiety, and marital discord compared to their healthy cohorts (15,21-23). Furthermore, male infertility treatment creates a significant burden to healthcare costs. Over 60% of men who pursue assisted reproductive treatments spend over \$15,000 out-of-pocket, and overall, these patients typically spent 16–20% of their annual incomes on infertility treatment in the US (24). Therefore, preventing iatrogenic male infertility, such as RE following pelvic sympathetic neurolysis in treating pelvic pain, is of great importance among interventional pain physicians.

Physiology of Ejaculation: The Role of Sympathetic Nervous System on Ejaculation

Ejaculation is divided into emission and expulsion (Fig. 1). Both phases are collectively under the control of the lumbar sympathetic nervous system and its network of conduits (i.e., the SHP, hypogastric plexus, and ending most caudally at the GI) that provide α -1 adrenergic innervation to the smooth muscle of the bladder neck, prostate, vas deferens, and seminal vesicles (25). During emission, the first phase of ejaculation, the prostate and seminal vesicle contract to deposit seminal fluid into the posterior urethra and simultaneously tighten the bladder neck by increasing the bladder neck tone in response to the increased sympathetic input (26). With the bladder neck tightly closed and the external urinary sphincter in a relaxed state, the semen is positioned to travel in the direction of least resistance (i.e., towards the urethral meatus). Following emission, the semen is propelled through the urethral meatus and out of the penis during expulsion. Sympathetic signals increase the bladder neck tone and prevent a retrograde flow of the semen into the bladder. Furthermore, sympathetic ganglia of T10-L2 along with parasympathetic sacral fibers carry sensory input to the ejaculatory centers in the brain (2 in the hypothalamus, medial preoptic and paraventricular nucleus, and one in the periaqueductal grey midbrain) (27).

Physiology of Ejaculation: The Role of Parasympathetic Nervous System on Ejaculation

Sacral nerve roots S2-4 give rise to the cavernous nerves of the penis, which are mainly parasympa-

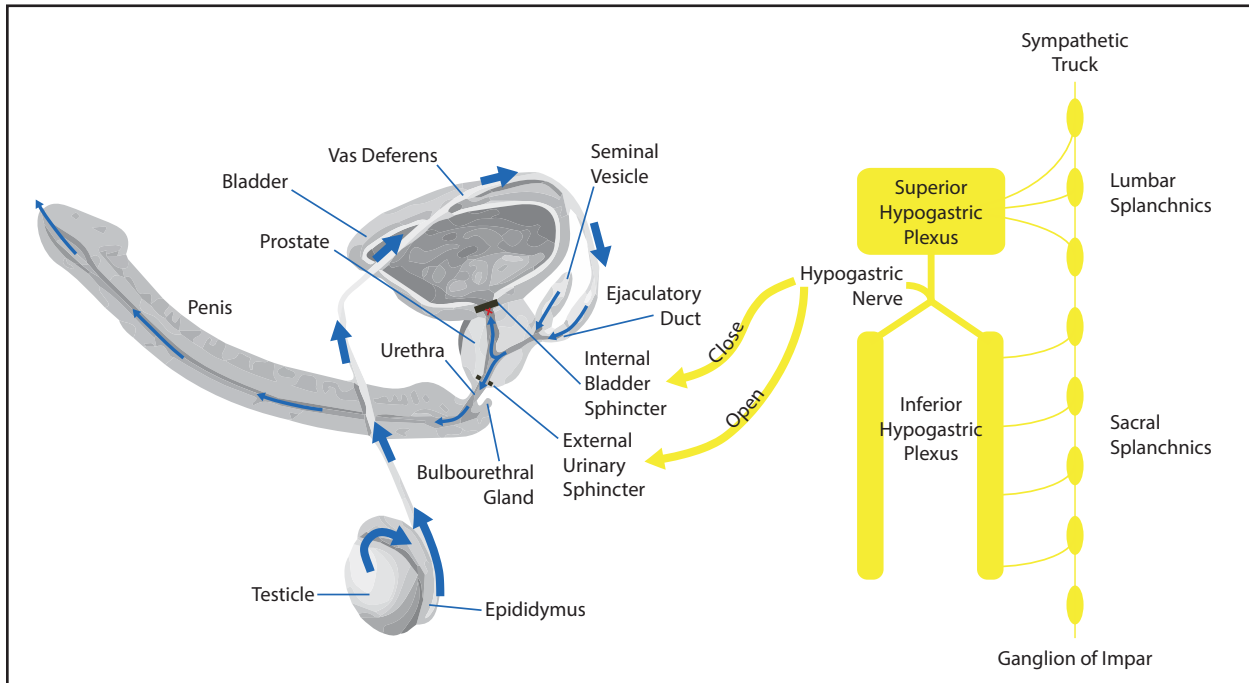


Fig. 1. A schematic representation of normal physiological ejaculation under sympathetic nervous system control.

thetic and responsible for the relaxation of smooth muscle, allowing blood to flow into cavernous spaces in the corpora of the penis, resulting in erection. Pudendal and pelvic nerves also contain somatic neurons from S2-S4 nerve roots that cause rhythmic contraction and relaxation of the ischiocavernosus, bulbospongiosus, and pelvic floor muscles to further facilitate antegrade semen emission (26).

Pathophysiology of Retrograde Ejaculation

In RE, bladder neck closure is impaired while all of the other elements of ejaculatory mechanisms remain intact. The retrograde semen trajectory will result in reduced expelled semen volume. When the semen volume is less than 2mL on at least 2 separate occasions, the diagnosis of RE and hypospermia should be considered (28). RE can occur partially (decreased ejaculate volume following orgasm) or completely (total absence of ejaculate i.e., aspermia). Clinically, patients may report dry orgasm or cloudy urine following orgasm. The diagnosis of RE is made by detecting the presence of spermatozoa or fructose in a post-ejaculatory urine sample (29,30). Causes of

RE can be grouped into 3 categories – mechanical, pharmacologic, and neurologic:

Mechanical – This is the most common cause of bladder neck injury leading to an incomplete closure, typically following transurethral resection of the prostate (TURP) (31) or the placement of surgical instrumentation to the lumbar spine (32). Lymph node dissections (33–36), colorectal surgery, lumbar sympathectomy, and retroperitoneal surgeries all carry a risk of causing collateral damage that could potentially lead to retrograde ejaculation (37). Damage to the SHP is also known to result in RE, urinary urgency, and incontinence (33–36). In addition to SHP, pudendal nerve injury can occur during pelvic surgeries (4,38)

Pharmacologic – α -receptor antagonists are the most common culprits causing RE due to their influence on the smooth muscle of the bladder neck and their ability to reduce tension. Tamsulosin, an α 1-adrenergic blocker, has been shown to significantly decrease bulbospongiosus muscular contraction force to expel semen in the antegrade direction

(39). Similarly, antipsychotic medications (i.e., chlorpromazine, thioridazine, and risperidone) are potent α 1-adrenergic receptor antagonists known to cause RE (40,41). Serotonin has been shown to affect a subset of inhibitory 5-HT receptors found in the seminal vesicles, vas deferens, urethra, and prostate to down-regulate ejaculation (42). Selective serotonin reuptake inhibitors (SSRI), such as fluoxetine and sertraline, increase the bioavailability of serotonin, potentially leading to RE

Neurologic – Stroke, multiple sclerosis, and chronic, uncontrolled diabetes can all lead to an autonomic neuropathy that may impair the sympathetic innervation of the bladder neck closure. Diabetic neuropathy is accountable for 5-18% cases of RE (37,43).

Chronic Pelvic Pain (CPP)

CPP is a broad diagnosis consisting of a variety of conditions and syndromes that appear to evolve into a neuropathic state that is typically recalcitrant to conservative measures (44). It affects both men and women with an estimated prevalence ranging from 4-40% (45). While the pathophysiology is still poorly

understood, there are a number of conditions known to increase one’s predilection toward developing it. In 2013, Hunter et al (44) extensively reviewed the pathophysiology and causes of CPP, including interstitial cystitis/painful bladder syndrome, coccydynia, anorectal pain, and chronic prostatitis/prostodynia (Table 1). Depending on the etiology, a typical treatment approach often begins with physical therapy, antibiotics, antidepressants, and/or oral analgesics. Failure of conservative therapies is almost inevitable in moderate to severe cases, thus requiring interventional pain procedures. While there is no consensus on what particular procedure or region should be targeted before another, 2 accepted targets are the GI and SHP (45).

Neurolytic Targets for Treating CPP

SHP

The SHP is a network of nerve fibers that originates from the T10-L2 (46). The SHP is located in the retroperitoneal space at the bifurcation of the aorta, merges on the anterior to the L5/S1 intervertebral disc, and travels caudally over the sacral promontory

Table 1. A summary of the pathological causes of pelvic pain (44).

Pathological Causes of Pelvic Pain	Highlights
Interstitial cystitis/painful bladder syndrome	*It is chronic and a diagnosis of exclusion with unknown etiology.
	*The likely causes: urothelial lining defects with exposure to mast cells (the most likely cause), autoimmune disorders, infection, pelvic floor dysfunction, toxins, and bladder wall defects.
	*It is characterized by frequency, urgency, dyspareunia, nocturia, and pelvic and/or abdominal pain.
	*It is diagnosed via cystoscopy, hydrodistention, and biopsy.
Chronic prostatitis/prostodynia	*Affects men
	*It is a diagnosis of exclusion.
	*The associated symptoms: frequency, dysuria, poor urinary flow, and genital or perineal pain.
	*4 categories of prostatitis, ranging from category I-IV, with category III being the most common type in men > 50 years of age and 3rd most common in those > 50 years of age.
Coccygodynia	*Coccygeal pain worsened by sitting.
	*The possible causes are trauma, infection, neoplasm, and osteoarthritis of sacrococcygeal joint or referred pain from the surrounding visceral structure and pelvic floor spasm.
Vulvodynia	*It is characterized by non-painful stimuli that result in painful sensation in the vulva.
	*There are several proposed mechanisms including increased muscle tone in superficial perineum and neurogenic inflammation.
Anorectal pain	*It is a diagnosis of exclusion.
	*It is often associated with levator ani syndrome, coccygodynia, and proctalgia fugax.
	*It is likely caused by neuropathic pain affecting the pelvic floor.

situated one cm from the midline and 2cm medial to the ureter and iliac artery (47). The SHP, which contains purely sympathetic fibers, continues to travel caudally and divides into bilateral hypogastric plexuses and eventually contributes to the lateral branches of the inferior hypogastric plexuses in the pelvis, while some splanchnic branches (S2-S4) make up the medial portion (48,49).

GI

The GI, also known as sacrococcygeal ganglion or ganglion of Walther, is a singular retroperitoneal structure located roughly at the level of the sacrococcygeal junction. The GI is the most caudal segment of the confluence of the 2 sacral sympathetic chains as they pass anteromedially over the sacrum, with some anatomical variability between the sacrococcygeal junction and the lower segment of the first coccyx (50). Pelvic splanchnic nerves carry parasympathetic nerve fibers to coalesce with sympathetic fibers at the level GI as well. The GI also contains visceral afferent signals from the perineum, distal rectum/anus, urethral and distal vagina/scrotum (51). Blocking the GI provides visceral and sympathetic pain relief from the perineal region (52–54).

Rationale for SHP/GI Neurolysis in the Treatment of CPP

Understanding the neuroanatomy in the lumbopelvic region provides the basis for targeting the sympathetic nervous system in treating CPP. Regardless of the pain source, the noxious stimuli of CPP can be transmitted via the sympathetic nervous system (i.e., SHP and/or GI) to the spinal cord then to the brain. Starting at the end organ, the afferent nociceptive signals travel up the unmyelinated postganglionic fibers toward the corresponding paravertebral ganglion and the gray rami communicans. At the paravertebral ganglion, the nociceptive stimuli may continue to propagate into the lateral grey column of the spinal cord through the myelinated fibers of the white rami communicans from T1-L2 into the spinal cord, or the stimuli may travel cephalad or caudal to a sympathetic paravertebral ganglion at the level(s) above or below before going into the spinal cord via the white rami communicans. The latter is specific to signals that originate caudal to L2 because white

rami communicans are absent below L2. The signals that originate caudal to L2 travel by postganglionic fibers to the corresponding grey rami communicans before joining the paravertebral sympathetic chain and continue cephalad until L2, or possibly higher, before transitioning to white rami communicans and spinal cord (44,55).

Bonica (56) first documented targeting the sympathetic nervous system in the management of CPP in 1954. In 1990, Plancarte et al (57) reported on the reduction of pain by 70% in malignancy-induced CPP through neurolysis of the SHP and recommended it as a superior target over the lumbar sympathetic chain. In the same year, Plancarte et al (11) also published similar outcomes of patients with perineal pain (malignant and nonmalignant) who underwent neurolysis of the GI. {AU: Ref. 58 is Reig et al; where does it belong?} In 2015, Ahmed et al (9) published a small study showing the efficacy of combined SHP and GI block for pelvic and/or perineal cancer pain with good relief without complications or serious side effects.

METHODS

CPP, like many pain syndromes, is responsive to nerve blocks, particularly those targeting the sympathetic nervous system (i.e., SHP and GI) (59,60). Similar to other chronic pain conditions, in cases where diagnostic blocks are only temporarily effective, neurolytic procedures are indicated as a means of potentially providing longer and more sustained relief (61). To our knowledge, there has not been any reported cases of RE as a consequence of combined or serial SHP and GI neurolysis, in any combination. We present a case series of 3 patients who reported RE consequent to a SHP blockade neurolysis following a GI neurolysis.

CASE SERIES

Patient 1 - JH

JH is a 29-year-old male with a 4-year history of CPP. The patient reported the pain began insidiously and without incident. At the time of the initial evaluation, he reported the symptoms localized to the penis, testicles, and perineum. The quality of the pain was sharp and “needle-like.” Neither a definitive diagnosis had been made for his pain or a precise mechanism for the symptoms.

His pain was erratic; however, sexual activity and sitting were the most predictable causes of pain. He tried several medications including acetaminophen-oxycodone, baclofen, diazepam, and alprazolam with minimal pain relief. Additionally, JH had tried a series of nerve blocks (pudendal and ilioinguinal) as well as physical therapy – none of which were successful. The patient underwent a GI block with near complete pain relief for several hours – no complications or side effects were noted. He underwent a subsequent GI neurolysis with 5cc of 98% dehydrated ethyl alcohol injected via the trans-sacroccygeal approach. Two weeks later the patient presented for a post-procedural follow-up at which time he reported no pain relief. The GI neurolysis was repeated one week later – this time the patient reported good relief lasting 5 to 6 months.

The pain returned 6 months later and had now spread to the inguinal region. The decision was made to repeat the GI neurolysis as well as perform a simultaneous neurolysis of the SHP in the hopes of capturing the inguinal pain – GI neurolysis utilized 5cc of 98% dehydrated alcohol; the SHP neurolysis (transdiscal approach) used a total of 14cc of 98% dehydrated alcohol (7cc on each side). One month later, the patient presented for follow-up. He reported near complete pain relief; however, he noted that when he achieved an orgasm during sexual activity there was no ejaculation. Eight months post-procedure, he continued to have this side effect. JH was evaluated by urology who subsequently diagnosed him with RE.

The patient was started on a combination of imipramine and midodrine that resolved the RE.

Patient 2 - SD

SD is a 44-year-old male with a 3-month history of pelvic pain. The patient reported the pain began shortly after the removal of a kidney stone that was lodged in an ejaculatory duct. The pain was sharp, shooting, and burning and radiated from his rectum to the tip of his penis and into his buttocks. It was worse with prolonged sitting and during sexual intercourse. He reported having tried a course of gabapentin that was only mildly effective. The patient underwent a GI block with near complete relief of his pain for several hours with no complications or unwanted side effects noted. Subsequently, he underwent a GI neurolysis

with 6cc of 98% dehydrated ethyl alcohol injected via the trans-sacroccygeal approach. Two weeks later, the patient presented for post-procedural follow-up. He reported the posterior, perineal pain was greatly improved. However, he still had a significant amount of pain at the tip of his penis.

Two weeks later, the patient presented for a SHP block – transdiscal approach with 14cc of 0.25% bupivacaine (7cc on each side). He reported that his pain improved by 50% for nearly 24 hours; however, he noted during that time he was unable to ejaculate when he achieved an orgasm. As the pain returned, he was once again able to ejaculate. The SHP block was repeated one week later with the same result; therefore, the decision was made to abort any plans for neurolysis to the SHP.

Patient 3 - MB

MB is a 24-year-old male with a 6-year history of CPP. The patient reported the pain started gradually as discomfort in the left testicle, without incident or trauma, accompanied by low libido and post-ejaculatory pain. Over time, the pain in the left testicle subsided, however he now complained of chronic pelvic floor pain and erectile dysfunction, as well as post-ejaculatory rectal/penile pain. No definitive diagnosis had been made for his pain or a precise mechanism for the symptoms.

He reported the pain radiated up the inguinal region during ejaculation and occasionally into the left leg. The patient received a GI block that provided good, albeit temporary relief to the pelvic floor and genital region; however, the pain radiating into the leg was unchanged – no complications or side effects were noted. A GI block was repeated one week later with the same result. Subsequently, he underwent a GI neurolysis with 3cc of 98% dehydrated ethyl alcohol injected via the trans-sacroccygeal approach. Two weeks later, the patient presented for post-procedural follow-up. He reported only transient relief from the GI neurolysis, thus the decision was made to proceed with a diagnostic block of the SHP.

After another 2 weeks, the patient presented for a SHP block – transdiscal approach with 14cc of 0.25% bupivacaine (7cc on each side). The patient followed-up one week later. He reported good relief of the majority of the areas of his pain for the remain-

der of the day after the block (approximately 10 to 12 hours). However, during that time he reported he was unable to ejaculate during orgasm. As the pain returned, his ability to ejaculate returned. The SHP block was repeated one week later with the same result; therefore, the decision was made to abort any plans for neurolysis to the SHP.

DISCUSSION

Ejaculation is a complex and synchronized process, coordinated by the sympathetic nervous system. Signals travel caudally from the lumbar sympathetic chains to SHP and GI into the bladder, testicles, and penis to initiate the emission phase of ejaculation and bladder neck closure under high pressure (37,62). This pressure gradient created by the bladder neck musculature ensures normal antegrade ejaculation in the direction of low-pressure urethral opening. In the pathological state, contractile expulsion force overcomes the low bladder neck closure pressure to cause a backward flow of semen into the bladder and results in RE. Permanent or temporary RE following neurological injuries to anterior lumbar spine such as bilateral lumbar sympathectomy or SHP injury are well-documented in the neurosurgical literature (63–69). Similarly, RE has also been described as a complication following interventional neurolytic procedures (70,71).

Traditional etiologies of RE are typically associated with α -receptor antagonists users, individuals with chronic, uncontrolled diabetes, or patients having undergone surgical procedures involving the prostate, bladder, and the like (72). Given that these patient populations are likely to be elderly and beyond the typical reproductive age, individuals that do not wish to father children, or in those with disabling terminal cancer pain in the pelvis, RE may not be a relevant complication or issue. Ahmed et al (9) published on findings of 9 men and 6 women, ranging from 41 to 67.6 years old, with cancer-related pelvic pain receiving chemical neurolysis. The authors described the plausibility that RE may be present but go undetected or unreported. However, in younger men that undergo interventional treatment for non-oncological pelvic pain, the prevention and education of the potential RE risk becomes significantly important, as it is much more likely to be noticed due to potentially heightened sexual activity by comparison.

RE is difficult to detect/diagnose in the overall male population due to similarities to other subtypes of male sexual dysfunction, as well as the potential for underreporting stemming from the fear social stigmatization (20). Some cases are simply unavoidable, despite the best efforts to avoid this dreaded complication; however, in cases of therapeutic neurolysis of the GI and/or SHP, RE can be predicted with the use of a diagnostic blockade beforehand.

Diagnostic blocks, as a whole, serve the following purposes: to confirm/negate a potential target as a pain generator and or conduit (thus assessing the utility of destroying it), to estimate the degree of pain relief, and to assess the risks for any potential side-effects or complications before applying irreversible neurolytic techniques. In the pelvic region, this is especially important as any reproductive and sexual dysfunctions not only cause detrimental psychosocial and reproductive impact to the patient, but the negative psychological consequences affect their partners and relationships as well (15,21–23).

This case series illustrates RE as a potential complication that should be considered when blocking the SHP following, or in tandem with, a GI neurolysis. It is the recommendation of the authors that if a neurolysis of either the SHP or GI has already been performed, and one is considering targeting the other for neurolysis, 2 repeated diagnostic blocks should be performed on separate visits to assess for RE, as well as any other potential complications. This is particularly important in male patients that desire or potentially would like to father a child in the future.

We recommend GI to be considered as the first neurolytic target in conditions summarized in Table 2 (73). In cases where GI neurolysis alone yields incomplete pain relief, SHP may be considered as an additional neurolytic target. However, we strongly recommend 2 repeated diagnostic blocks of the SHP be performed with 0.25% or 0.5% bupivacaine as a precursor to neurolysis. Additionally, we recommend the patient, if possible, to engage in either sexual intercourse or masturbation within 6 to 8 hours of the block, as a means of potentially detecting RE during the time period while the SHP is under the influence of a sodium channel blocker. The presence of cloudy urine, fructose in the urine, and ejaculate volume less than 2mL following the SHP blockage suggests RE.

Table 2. Conditions in which GI blockade is considered as a first line in interventional pain procedure (73)

Perineal pain, with or without malignancy	Endometriosis
Rectal/anal pain (proctitis)	Chronic prostatitis
Distal urethral pain	Proctalgia Fugax
Vulvodynia	Coccygodynia
Scrotal pain	Radiation proctitis
Female pelvic/vaginal pain (distal 1/3)	Posttherpetic neuralgia
Localized, burning perineal pain associated with urgency	Sympathetically-maintained pain (i.e., Complex Regional Pain Syndrome)

In such cases where RE is suspected, using irreversible neurolytic agents such as phenol or dehydrated alcohol should be avoided to prevent permanent RE. If CPP severity necessitates additional interventions, pulsed radiofrequency ablation is a reasonable neurolytic alternative that could preferentially target A- β or c-fibers to interrupt pain signals, while leaving fibers responsible for physiologic ejaculation intact (74–76). Spinal cord stimulation at T11-T12 (77), dorsal root ganglion stimulation (78), or pudendal nerve stimulation (79) may also serve as a viable option in patients who are unresponsive to other treatments.

CONCLUSION

RE is a potential consequence of combined or serial SHP and GI neurolysis; consequently, SHP and GI neurolysis should not be performed simultaneously. In patients where the GI has already been ablated, one should proceed with caution when considering interventions targeting the SHP – and reverse in cases where neurolysis of the SHP occurred first. If after neurolysis of one structure has already occurred, and the other is being considered in the pursuit of more complete pain relief, 2 diagnostic blocks should be performed before any neurolysis to assess for the possibility of RE.

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