REVIEW PAPER

UROLITHIASIS

Evolving types of pudendal neuromodulation for lower urinary tract dysfunction

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Introduction Sacral neuromodulation and posterior tibial nerve stimulation for lower urinary tract dysfunction (LUTD) and overactive bladder yield good and reliable results. However, neuromodulation research is continuously evolving because there is still need for more patient-friendly treatment options in the therapeutic management of LUTD. Pudendal neuromodulation (PNM) has been emerging as a promising alternative treatment option for the last few decades. The aim of this study is to review the current state of the art of PNM.

Material and methods A wide literature search was conducted in the field of PNM using Medline through the PubMed database and Elsevier using the Scopus database; a critical review of the results was then carried out. PNM has been studied in its various possible aspects: percutaneous PNM, transrectal/transvaginal PNM, and both percutaneous and transcutaneous dorsal genital nerve stimulation.

Results Each technique was found to result in promising improvements in different clinical outcomes, with some trials reporting even better results than sacral neuromodulation.

Conclusions As a result of a comparison between the various PNM techniques with both sacral neuromodulation and posterior tibial nerve stimulation, we think that PNM should be seen as seriously promising, and we believe it will expand the treatment options for overactive bladder. Even though several studies accordingly showed PNM to be safe and effective, a systematic review and meta-analysis were not feasible. PNM in its various techniques is a promising treatment for LUTD. Nevertheless, further research is needed to include it in treatment algorithms.

Key Words: pudendal neuromodulation ‹› lower urinary tract dysfunction ‹› overactive bladder ‹› neuromodulation ‹› sacral neuromodulation ‹› posterior tibial nerve stimulation

INTRODUCTION

Overactive bladder (OAB), defined by the International Continence Society as ‘a syndrome characterized by urgency with or without urgency incontinence, usually with frequency and nocturia’, affects approximately 16.5% of adults [1]. It affects tens of millions of people worldwide, necessitating an economic burden through treatment costs [2]. Furthermore, lower urinary tract dysfunction (LUTD) has a profound negative impact on the quality of life.

Nevertheless, first-line conservative treatments such as antimuscarinic agent therapy do not always lead to sufficient improvement in symptoms of OAB and are often associated with disabling adverse effects [3] with discontinuation rates nearing 50% in the first month of treatment [4, 5].

Electrical stimulation of the sacral roots, generically described as ‘neuromodulation’, has emerged as an alternative and attractive treatment for refractory OAB [4]. Research towards neuromodulation for overactive bladder (OAB) has been increasing over the past decades [6].

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Sacral neuromodulation (SNM) and posterior tibial nerve stimulation (PTNS) are effective and safe third-line treatments for OAB. Their overall success rates range from 43 to 85% and 40 to 79.5%, respectively [7]. SNM has been used for refractory OAB 'dry' (without urinary incontinence) and 'wet' (with urinary incontinence) for more than 2 decades, with success rates of 70–80%, similar to those of intravesical botulinum toxin [8]. Since the approval of InterStim therapy by European Conformity (CE) (1995) and the Food and Drug Administration (FDA) (1997), SNM has become an established advanced treatment option for OAB, which has treated more than 375,000 patients worldwide [9].

Nevertheless, both SNM and PTNS rarely completely alleviate the initial symptoms. Another limitation is the reoperation rate of 30% to 40% [10] in SNM, while PTNS treatment requires frequent outpatient visits for administration. The future holds great promise for new and improved treatment methods for this pervasive, costly condition. A recent review highlighted that there is still a need for more patient-friendly treatment options for OAB [2021,11]. Therefore, several new neuromodulation modalities have been studied in the last decades, besides the 2 abovementioned, which are the most studied. Many of them yield promising results; however, they are yet to be implemented and have to live up to the current standard of care. It is hypothesized that SNM works by inhibiting the voiding reflex by means of electrical stimulation of sensory afferent fibres. Many of the sensory afferent nerve fibres contained in the sacral plexus transmit signals from the pudendal nerve [12]. The urethra is predominantly innervated by the pudendal nerve, mostly known for its motor control of the external urethral sphincter (EUS) and the sensory control of the perineal area [13]. Therefore, theoretically, it is not surprising that direct stimulation of the pudendal nerve has been reported to be effective for bladder inhibition [12]. We refer to this as pudendal neuromodulation (PNM), and it is the most studied neuromodulation modality after SNM and PTNS.

Only 7% of patients with bothersome urgency urinary incontinence (UUI) were found to be treated with any third-line treatments. Hence, Bretschneider et al. highlighted the need for improved treatment algorithms to escalate patients with persistent symptoms, or to adjust care in those who have been unsuccessfully treated [5].

The purpose of this manuscript is to address the available literature advancements in PNM and to present its current state of the art.

MATERIAL AND METHODS

A literature search was conducted on Medline using the PubMed database and Elsevier using the Scopus database in March 2023. The search strategy was based on the following keywords: 'overactive bladder', 'lower urinary tract dysfunction', 'pudendal nerve stimulation', 'pudendal neuromodulation', 'pudendal nerve', 'dorsal genital nerve stimulation', and 'lower urinary tract dysfunction', and it was conducted according to the PRISMA 2020 guidelines [14]. Articles were included according to inclusion criteria (randomized controlled trials, prospective trials, large retrospective studies) and exclusion criteria (case reports, outcomes not clearly expressed in full text). The references lists of the included studies were also scanned. We limited the search to reviews and studies with accessible full text in the English language. The authors independently assessed all the found articles for possible biases, and a collective decision was made whether to include those deemed at high risk due to missing results or unclear methodology. The included studied were grouped according to treatment modality. The present review was not registered, and no protocol was required. No sources of financial or non-financial support were available or needed for this review. The authors declare they have no competing interest in the review. For any enquiries (e.g. data availability, data extraction details, etc.) please contact the Corresponding Author.

RESULTS

Twenty articles out of 83 were included in the review, which are shown in the following subchapters (16 relative to pudendal neuromodulation and 4 to dorsal genital nerve stimulation).

Clinical studies on pudendal neuromodulation

Since the late 1980s, PNM has been used as a treatment modality for LUTD, including OAB, urgency and stress urinary incontinence (UUI and SUI), and neurogenic LUTD. Ohlsson et al. treated 29 OAB patients with 4 sessions of maximal electrical stimulation of the pudendal nerve, finding a significant increase in functional bladder capacity and a decrease in the frequency of micturition with no severe side effects [15].

Later, in the early 2000s, prolonged PNM was made possible after Bion-r therapy (Advanced Bionics Corp., Valencia, California) was introduced as a new minimally invasive option for effective neuromodulation [16]. The Bion-r is a self-contained, battery-powered, telemetrically programmable, current-controlled mini-stimulator with an integrated electrode. It can be implanted adjacent to the pudendal nerve at Alcock's canal and be used to directly stimulate the adjacent excitable tissue. Bosch, Groen et al. treated 16 refractory OAB-wet women between 2004 and 2005 [16, 17, 18] with PNM administered through the Bion-r device. The number of incontinence episodes and pads used per day as well as the leakage severity index decreased considerably. However, the use of the device was discontinued, and it never reached the market in the USA.

In 2007 [19] and 2014 [20] laparoscopic techniques for direct endopelvic PNM were described, and then in 2018 [21], a laparoscopic technique for combined SNM and PNM. Both techniques were reported as yielding promising results, with the latter stating PNM to have better results than SNM because it improved urinary and faecal incontinence by direct inhibition of the bladder and rectum and by selective contraction of the anal and urethral sphincters without activation of other nerve fibres in the sacral nerve roots. Nevertheless, the major limitations were the requirement of general anaesthesia and the very small number of case reports published.

In its endopelvic portion, the pudendal nerve is difficult and dangerous to reach using percutaneous puncture techniques because it is located deep within the pelvis and in proximity to the sciatic nerve and major pelvic veins [4]. Hence, the extrapelvic portion of the nerve was preferred for most of the subsequent studies, either percutaneously or with a combined percutaneous and endoscopic approach.

Fifteen neurogenic OAB patients successfully received a percutaneous lead placement to the pudendal nerve and obtained clinical improvement with PNM performed by Spinelli et al. The percutaneous implant was feasible when using the tools used for SNM (i.e. Interstim 3023, Medtronic, Minneapolis, USA), with the correct positioning of the electrode being ensured by neurophysiological intraoperative monitoring. According to the authors, chronic PNM offers a therapeutic alternative for patients affected by neurogenic OAB, which are known to respond worse to SNM and antimuscarinic drugs, and it can take place before using alternatives such as botulinum toxin or major surgery such as bladder augmentation. Furthermore, it is reversible, and the lead can be easily removed if the stimulation is not successful [22]. Nevertheless, one of the drawbacks of such technique is the requirement to use oscilloscope recordings to find the nerve.

An important step forward with PNM was achieved in 2005, when it was chosen as a superior lead in 79.2% of 24 patients with voiding dysfunction simultaneously implanted with pudendal and sacral leads by Peters et al. [23] in a randomized, blinded, crossover trial comparing PNM and SNM. Seventeen of the 24 initial patients were also diagnosed with refractory interstitial cystitis and followed up for 6 months [24]. Comparable to immediately after the treatment, PNM was chosen as the better lead in 77% of patients after 6 months. Hence, PNM was claimed to be an alternative approach to treat voiding dysfunction.

Ninety-five refractory SUI women successfully underwent percutaneous PNM placement in 2012 [25], treated by Wang et al. They proved that the lead placement by an experienced surgeon positively influenced the results as compared as the results of leads placed by an unskilled surgeon (study arm conceived as placebo control group) and showed a satisfactory overall efficacy. A study by the same research group, published in 2016, showed that PNM was significantly more effective in treating 21 women with SUI as compared to another 21 women treated with pelvic floor muscle training and transvaginal electrical stimulation (TES) [26].

Similarly, PNM yielded better results when compared to TES alone in treating, respectively, 80 vs. 40 refractory UUI women in 2017 [27] and when compared to anogenital electrical stimulation for 60 neurogenic LUTD patients in 2018 (40 vs. 20 patients, respectively) [28].

In 2018 [29], Lemos et al. attempted to reduce the risk of damaging the deep neurovascular bundles and the ramifications of the internal pudendal vein and artery by changing the needle access. The needling was shifted approximately 1 cm cranially and medially to the ischial tuberosity at a 45° angle towards the median sagittal plane, and they found that they could stimulate the pudendal nerve accurately, concluding that their technique might be useful. However, they stated that their technique requires further exploration in greater samples.

In 2019, Jottard et al. [30] explored the feasibility of the ENTRAMI technique (sacral transforaminal lead placement under full visual control by trans gluteal endoscopic guidance). In their publication they describe promising feasibility results of 8 dissections with the ENTRAMI technique performed on 4 human cadavers, allowing both PNM and SNM. They claimed the transforaminal approach to be superior to the transgluteal or perineal puncture site due to the intrapelvic rather than subcutaneous course of the lead, making it less prone to migration when flexing the hip, and because the pudendal vessels and nerve can be clearly identified, reducing the risk of damaging them during a blind, percutaneous

technique. Published literature on the ENTRAMI technique, however, is very scarce, only reported to having been performed in few living patients (not for voiding dysfunction but for chronic pain), and all published cases were performed by the same experienced surgical team.
Gu et al. [31] tried a novel technique designed to assist the surgeon in placing the lead, achieving the closest position to the pudendal nerve with the lowest possible risk of damaging other organs, under the guidance of a 3D printed model. They successfully treated 16 patients, describing the surgical method as accurate, reversible, efficient, and minimally invasive. However, a major limitation is that MRI of the pudendal nerve is difficult to obtain, different scanning parameters are required, and 8 h of MRI monitoring were required to obtain the scanning parameters needed to perform the procedure.
Despite the encouraging results with PNM, difficulties in lead placement and a high rate of secondary lead migration impedes its clinical implementation. Subsequent attempts to treat LUTD via neuromodulation were done either directly to the pudendal nerve or to its most distal branch, known as the dorsal genital nerve (DGN), which is suspected to modulate the lower urinary tract through post-synaptic or presynaptic inhibition of bladder afferents. [2]

Dorsal genital nerve stimulation

Percutaneous

In 2008 [32], 19 women with UUI were successfully treated with a 7-day home period of percutaneous DGN stimulation (pDGNS). The lead placement was performed under local anaesthesia and was well tolerated by all subjects without the need for fluoroscopy. After a week of stimulation, 76% of subjects had a ≥ 50% reduction in pad weights and 47% of subjects were completely dry. Improvements were also observed in the number of heavy incontinence events (IE) and severity of urgency events.
Similar results were reported by Van Breda et al. [33] in their feasibility study. The authors implanted a percutaneous DGN lead in 7 patients with non-neurogenic OAB, training them to self-administer the stimulation on demand (being a perceived voiding desire, the stimulus inducing the subject to activate the electrical stimulation) to inhibit an involuntary detrusor contraction. The results indicated that subject-controlled, on-demand pDGNS is possible over a longer period, in a home setting, with a positive effect on non-neurogenic OAB symptoms with UUI. Although the placement is an easy procedure, it is difficult to fixate the electrode to keep it in the correct position. Improvements in hardware, such as a better fixated electrode and an easy-to-control stimulator, were deemed necessary to make on-demand DGN stimulation a clinically applicable treatment possibility.

Transcutaneous

Fjorback et al. [34] showed that undesired detrusor contractions can be suppressed by using an event-driven transcutaneous DGNS (tDGNS) in 8 patients with multiple sclerosis. The event leading to the activation of tDGNS was set as a detrusor pressure above 10 cmH2O.The bladder capacity increased, and the number of incontinence episodes decreased.
On-demand, intermittent, and continuous tDGNS may be safe and practical to manage neurogenic detrusor overactivity following spinal cord injury, as demonstrated by Doherty et al., who found that tDGNS increased the time between the first detrusor contraction and the first desire to void, giving the patient enough time to reach the toilet and preventing UUI episodes with no severe side effects [35].

DISCUSSION

At the time of a robust review by Bartley et al. in 2013 [36], PNM was concluded to be an effective treatment of OAB, with success rates of up to 90%, and it was deemed an alternative treatment of OAB, with success rates of up to 90%, and an alternative option for patients refractory to SNM. A review from Kannan et al. found that PNM gives promising results as compared to sham stimulation in treating post prostatectomy UUI (2018 [37]); however, this evidence was of moderate GRADE quality. Some reports indicate PNM to be superior to SNM in treating refractory OAB. Almost all who failed SNM responded to PNM (93.2%). Overall, a positive PNM response was achieved in 71% of participants who underwent PNM for refractory interstitial cystitis and/or OAB [38]. In another study, after temporary stimulation of the pudendal nerve or sacral roots, most of the patients preferred PNM to SNM [10]. According to Marinkovic's personal experience with PNM for OAB, it is a welcome addition for failed-SNM patients, where a 78% success rate was achieved in 26 patients after 5-year follow up. This highlighted the need for PNM to be prospectively studied, with approval sought for its implementation when tertiary treatment fails and a potential secondary OAB treatment when second-line medical treatment fails [2].
The results of the present review show that there are several promising PNM techniques that have been

investigated, some of which have the potential to expand the neuromodulation options for OAB.

The currently clinically available and most used neuromodulation techniques, SNM and PTNS, have several limitations. The main obstacle of SNM is the requirement of general anaesthesia, and for PTNS it is frequent hospital visits for its administration. They both require regular control visits to monitor and adjust the stimulation settings.

The advantages of course do not come without drawbacks: the low quality of literature evidence and the small size of study populations in the described techniques pose as a limitation to the therapeutic field that PNM could cover. The reviewed articles widely vary in terms of outcomes, study designs, length of follow-up, and overall methodological quality, making a meta-analysis of results not feasible.

Nevertheless, we believe that the results should be interpreted as seriously promising, although we recognize a major limitation in the lack of quality of evidence of the reviewed articles, as well as the narrative rather than systematic nature of the present review. The lack of solid bases is counterbalanced by promising clinical results, notably in those cases where previous standard-of-care treatments have failed. An important result comes from the head-to-head, blinded, crossover comparison between SNM and PNM, resulting in a vast patient preference towards PNM. These results could reasonably make PNM an interesting, cutting-edge treatment option for OAB patients. The main advantages of PNM, when comparing the results to those of SNM, are superior clinical results, good tolerance by patients, and ease of performing treatment in an ambulatory or even a home setting.

Contrary to SNM, most of the described PNM techniques are performed under local anaesthesia and can be performed in day-care, and most of them even during an outpatient clinic visit. This contributes towards the aforementioned need for more patient-friendly treatment options for OAB [11].

Should PNM gain more evidence of safety and efficacy and grow in popularity among urologists, its position within the treatment algorithm of OAB would remain to be defined. Considering that only a fraction of OAB patients will be treated with any third-line treatments [5], we believe that the treatment algorithms to escalate patients with persistent OAB symptoms could include PNM in the future. This could be before the escalation to the current third-line treatment or as an addition for patients who did not respond to sacral neuromodulation, as suggested by Marinkovic [2].

A possible reason for the claimed superiority of PNM over SNM is that the pudendal afferent nerves play a key role in inhibiting the voiding reflex. While sacral neurostimulation excites a select few pudendal afferent nerves, direct neurostimulation of the pudendal nerve itself may be superior in suppressing this voiding reflex [2].

Despite all the recognized limitations of the available literature, bearing in mind the results of PNM together with its pros and cons, a head-to-head comparison between it and the currently available neuromodulation techniques could reasonably lead to PNM proving to be less invasive but efficacious where the other treatment options often fail. Indeed, PNM was chosen over SNM in most patients and with less impact on daily activities for both the patient and the urologist – as compared to PTNS – with fewer office visits needed for PNM (although a head-to-head comparison to answer this interesting question has not been carried out).

CONCLUSIONS

The stimulation of the pudendal and dorsal genital nerves to modulate lower urinary tract symptoms is a promising treatment modality. The current techniques that do so have shown to be feasible, safe, and efficacious. However, evidence is limited, and only small samples have been compared. Consequently, neither the EAU nor the AUA guidelines recommend use of PNM. No PNM devices have received approval by any local regulatory agency such as the FDA or EMA (European Medicines Agency). This review highlights the promising results of PNM for the treatment of OAB which is encountered daily by urologists and can be very bothersome for patients. Further efforts are to be done on this topic, preferably using a larger population and possibly by prospectively randomizing patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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