Sacral and Percutaneous Tibial Nerve Stimulation, Stem Cell Therapy, and Transanal Irrigation Device

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10.1 Sacral Nerve Stimulation

The early experiences with sacral nerve stimulation for refractory overactive bladder (OAB) [1] by urologists stimulated colorectal surgeons to use this procedure also for bowel dysfunctions, such as fecal incontinence (FI) [2] and chronic constipation (CC) [3, 4]. The first experience for FI was described by Matzel [2], and then the International Consultation on Incontinence in 2013 introduced sacral nerve stimulation (SNS) as a first-line treatment for FI in patients without or with minimal sphincter defect and as a second choice in those with moderate or large defects [5].

10.1.1 How It Works

The sacral nerves S2–S4 modulate pelvic sensitivity and the motility of the urologic and gastrointestinal functions of the pelvic floor. Electrical stimulation of the sacral roots creates a modulation of motor, sensory and autonomous nerve pathways in both the peripheral and central system, accounting for good outcomes in such different conditions as FI, CC, OAB, urinary incontinence, and low anterior resection syndrome (LARS) [6].

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10.1.2 Patient Selection

Patients with prevalent active fecal incontinence are the best candidates, even if they have a damaged sphincter [7]. A large group of patients may have associated symptoms such as urinary incontinence, chronic pelvic pain or CC, which may also improve with SNS. Patients are instructed to keep a bowel diary before and during the trial stimulation, which can last for 4–8 weeks. A $\geq$ 50% improvement following the trial period is considered good, leading to the definitive implant. The contraindications for SNS are the need for magnetic resonance (MR) or therapeutic ultrasound, sacral skin sepsis, pregnancy or uncompliant patients. In 2020 MR-compatible devices, also with a rechargeable stimulator, were made available, which has extended the surgical indications.

10.1.3 Surgical Procedure

The procedure requires fluoroscopy. The patient lies in a prone position with the legs lower than the pelvis and a pillow under the lower abdomen to straighten the sacral curvature. The SNS trial may be performed using a temporary or a permanent electrode. In the first case, the temporary electrode remains connected to a stimulator for 14 days and is then removed; in the case of a permanent tined lead electrode, the definitive stimulator may be implanted 4–6 weeks after the trial stimulation. The procedure is generally performed under local anesthesia so as to allow testing of the sensory perception of flutter/vibration in the anovaginal/scrotal region or motor response.

The first step involves placing the needle in both S3 foramina, testing the response and choosing the better side. Then, the electrode is positioned with three poles placed further inside the medial sacral surface and connected through a subcutaneous tunnel with an external stimulator. In the case of failure, both the external stimulator and the electrode are removed, taking care to do this slowly and checking that that the electrode is intact. In the case of a good response, instead, only the external connection is removed and the implantable stimulator is placed in the subcutaneous tissue, generally on the contralateral side to the electrode.

10.1.4 Complications

The most frequent complications are pain at the site of the implant, infection, and loss of efficacy occurring early (within 1 year) or after 2 years or more requiring surgical revision in 33% [8]. The pain at the site of the implant is managed by changing the site or the depth of stimulator placement. Local infection requires removal of all devices and planning a second implant after wound healing (at least 6 months). Sometimes the tined lead records high impedance during the follow-up and may be a cause of failure. In this case, simultaneous explantation and repositioning of a new electrode may solve the problem.

10.2 Percutaneous Tibial Nerve Stimulation

The first uses of tibial nerve stimulation (TNS) methods were reported in 1983 [9] through adhesive electrodes and then in 1999 [10] through needle electrodes in posterior tibial nerve stimulation (PTNS) to treat urinary dysfunctions such as lower urinary tract symptoms or OAB.

10.2.1 Procedure

The original technique consists of placing a 34-gauge needle in the lower leg, 3–4 cm above the medial malleolus and a grounding pad on the ipsilateral calcaneus. The patient lies supine with the knees adducted and flexed (frog position). Generally, the current levels have a range of 0.5–0.9 mA at 10–20 Hz and a pulse width of 200 μs and the intensity of the current is adjusted to the patient's motor response often visible from the flexion of the big toe or extension of the entire foot or on the sensory response in the ankle area or on the sole of the foot.

Although some studies have shown the efficacy of TNS for both urinary and bowel dysfunctions, PTNS has been hypothesized to be more effective as the proximity of the needle to the tibial nerve attenuates the effect of skin impedance, and lower current intensities are sufficient to have a sensory and motor stimulation [11]. The duration of the treatment is about 20–30 min while the frequency of the treatments can be variable [12]. Some authors have already hypothesized that longer or more frequent treatments yield faster results [13].

10.2.2 Literature Results

Thomas et al. randomized 30 patients with fecal incontinence to receive treatment once a day or twice a week and demonstrated that patients in the daily group experienced a significant improvement in lifestyle and embarrassment on the Rockwood FI quality of life (QoL) assessment [14]. The actual benefits of PTNS on FI treatment are not yet reliably established. In 2015, Knowles et al. randomized 227 patients to receive PTNS or sham stimulation failing to demonstrate any effective benefit of PTNS to treat FI in adults [15]. The most recent results on PTNS use are more encouraging, as in most studies the manometric results intended as resting pressure and squeeze pressure and the Wexner score after treatment were improved [16, 17]. In a trial by Solon et al., 81 patients with FI performed PTNS with an 80% success rate. In these patients the rates of FI and defecatory urgency were significantly reduced in the first year and remained so until the end of the 2-year follow-up, also leading to an improvement in QoL [18].

10.3 Stem Cell Therapy

The current application of mesenchymal stem cells (MSCs) has its origin in the experiments of Caplan in 1991, who demonstrated that bone marrow (BM) transplantation into different sites induces a de novo ectopic bone and marrow [19].

BM, as well as adipose tissue (AT), dental pulp, and umbilical cord, is a source of MSCs/progenitor cells, but AT represents the ideal source due to the high concentration of regenerative cells, easy access and low risk associated with autologous therapies. Owing to these characteristics, new processing devices have now been developed and made available on the market to obtain ready-to-use, minimally manipulated autologous MSCs, such as Lipogems (Lipogems International S.p.A., Milan, Italy) [20].

In recent decades the use of human MSCs derived from AT has spread in different surgical fields [21], with a recent application to treat AI [22]. The whole surgical procedure including pre- and post-treatment 3D 360° transanal ultrasound has already been described [23].

However, autologous AT currently represents least common source of MSCs for AI treatment. In fact, in a recent review the most frequent sites were skeletal muscle and BM. In 44 studies, MSCs originated from muscle in 28 studies (17 skeletal and 11 smooth), from BM in 10, and from AT in 6. Eight studies used neural cells for bioengineered constructs and one publication used umbilical cord [24].

Hence, the overall preclinical and clinical results have demonstrated the safety of MSCs to treat AI. Although the preliminary results were highly promising, only three studies were controlled with placebo injection. Further studies are therefore needed to identify the source of MSCs guaranteeing the best outcome, considering the costs and the patient's involvement.

10.4 Transanal Irrigation

Transanal irrigation (TAI), also known as retrograde irrigation (RI), represents an alternative approach to the management of FI after the failure of conservative therapy or as additional treatment after surgical treatment. The use of this method goes back in time, and the control of continence with irrigation or enema was the first treatment described in history. In recent times, TAI was first used in 1987 in children with spina bifida suffering from FI. Subsequently, its use also spread for other disorders and in 1989 Iwama et al. used a conventional colostomy irrigation set through the anus in order to clean the last part of the colon in patients with defecatory urgency and impaired bowel control after low anterior resection [25]. The main goal of TAI is to restore a regular bowel routine and, for this reason, its field of application has expanded, with TAI being used for a series of intestinal dysfunctions ranging from incontinence, constipation, neurogenic diseases, up to LARS [26].

10.4.1 Procedure

The patient, sitting on the toilet, can autonomously introduce a short probe into the rectum through the anus. The probe is connected to a plastic bag that can be filled with lukewarm tap water. With a balloon catheter delivery system, once the catheter is inserted, the balloon is inflated inside the rectum, which allows continence to be maintained during administration of the enema. With a cone delivery system, the cone has to be held in place during instillation of the irrigation fluid and the patient needs a degree of flexibility. The water is instilled either by gravity or by means of a pump that the patient can activate or deactivate differently depending on the model. It is common to consider 400–500 cm^3 of warm water to be an appropriate starting volume for irrigation in adults [27] but there is little evidence in the literature about optimal irrigation volumes. A randomized trial compared high- and low-volume irrigations in adult patients with CC [28] but the volume of water and the frequency of administrations can vary depending on the patient's requirements and bowel disorder.

10.4.2 How It Works

TAI does not appear to alter the function of the anorectal sphincter but rather it increases rectal tolerability and its distension. One study found that, in patients with FI treated with TAI, the resting and squeeze pressures were relatively lower in the follow-up. This finding, however, is to be attributed to the course of the disease rather than to TAI as the patients with CC treated with TAI did not show any alteration of sphincter function [29]. TAI is a type of treatment that requires the patients' commitment but has relatively rare side effects and can be stopped or resumed at any time. It is also relatively cheap and the training can be delivered entirely by the nursing staff without the aid of a doctor [30].

10.4.3 Literature Results

Most published studies analyze the efficacy of TAI simultaneously on FI and CC [31]. Alterations in lifestyle, coping, depression, social isolation and embarrassment are the fundamental elements lowering the QoL of patients suffering from FI [32]. Although most of the studies do not use validated questionnaires, the results tend to suggest an increase in the QoL of patients who perform TAI [30, 33]. In 2006, Christensen et al. found that TAI improved symptoms related to QoL in spinal cord–injured patients [34]; more recently, other studies have confirmed the marked improvement in QoL also in other categories of defecatory disorders [35, 36] and in patients with LARS [37]. Although it has generally been shown that TAI increases the QoL of patients with defecatory dysfunction, the drop-out rate with this therapy is still very high and, in some series, less than 50% of patients continued TAI [38]. The main reasons are dislike of the treatment, resolution of the symptoms, time

consumption, side effects, and practical problems such as fluid leakage or catheter expulsion [33, 39]. Recently, a retrospective series of 108 patients analyzed the predictors of compliance in the treatment of fecal disorders. In this study, patients with FI gave the best results and 54.5% remained compliant with TAI. In the analysis of predictive factors, training sessions were found to be the only factor that predicts patient compliance with TAI [38]. Patient education in TAI remains a key step in this treatment. Although the procedure is in most cases well tolerated and easy to perform, some cases of rectal and enterovaginal perforations have been described [36, 40]. A recent global audit that collected data from 2005 to 2013 has estimated a risk of perforation of less than 2 per million procedures [41]. Professional nurses experienced in the field of TAI have the task of carefully selecting motivated patients and instructing them by explaining the procedure and any relative and absolute contraindications.

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