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Pudendal Neuralgia: A New Option for Treatment? Preliminary Results on Feasibility and Efficacy

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Abstract

Objective. The aim of this prospective study was to investigate the feasibility and report the short-term results of a new procedure for treatment of pudendal neuralgia, consisting of transperineal injections of autologous adipose tissue with stem cells along the Alcock's canal.

Methods. Fifteen women with pudendal neuralgia not responsive to 3-months medical therapy were examined clinically, with VAS score, validated SF-36 questionnaire, and pudendal nerve motor terminal latency (PNMTL). These patients were submitted to pudendal nerve lipofilling. Clinical examinations with VAS, SF36, and PNTML were scheduled during 12 months follow-up, with the incidence of pain recurrence (VAS > 5) as primary outcome measure. Appropriate tests were used for statistics.

Results. All patients had preoperative increase of pudendal nerve latencies. Twelve patients completed the follow-up protocol. There was no mortality, and no complications. Two patients had no pain improvement and continued to use analgesic drugs. At 12 months VAS significantly improved (3.2 ± 0.6 vs 8.1 ± 0.9, $P < 0.001$), as well SF36 (75.5 ± 4.1 vs 85.0 ± 4.5 preoperative, $P < 0.01$), while PNTML showed a nonsignificant trend to a better nerve conduction (2.64 ± 0.04 vs 2.75 ± 0.03 preoperative, $P = 0.06$).

Conclusions. The new technique seems to be easy, with low risk of complications, and with significant improvement of symptoms in the short period. A larger study with appropriate controls and longer follow-up is now needed to assess its real effectiveness

Key Words. Pudendal Neuralgia; Lipofilling; Stem Cells

Introduction

Pudendal neuralgia is an increasing multifactorial condition, with a heavy impact on patient's quality of life. It consists of chronic perineal pain along the course of pudendal nerve, variably described by the patient, as mono, or bilateral, sometimes radiating to gluteus, genitals, or thighs [1]. The incidence is documented at 1% of the general population and women are more frequently affected than men [2]. Recognized causes of pudendal neuralgia are floor muscle spasm, entrapment from sacrospinous, or sacrotuberous ligaments, pelvic trauma, or pelvic surgery (mesh, suture, or staples

directly injuring the nerve) [3]. Diagnostic criteria were defined at the Nantes Consensus Conference in 2006. Five essential criteria must all be present: pain limited to the territory of innervation of pudendal nerve, pain predominant during sitting, pain does not awaken patient from sleep, no objective sensory defects, positive effect of anesthetic infiltration of the pudendal nerve. Sensation of foreign rectal (or vaginal) body and worsening of pain during defecation, pain predominantly unilateral, and worsening throughout the day are complementary signs [4].

Clinical diagnosis may be confirmed by anal electromyography (EMG), anorectal manometry, pudendal nerve terminal motor latency, but these tests are not considered necessary for the diagnosis, as none is specific [5].

Current treatments for pudendal neuralgia are analgesics or neuroactive drugs, pudendal nerve block, neuromodulation, and surgical decompression, but none of these treatments is completely satisfactory, or definitely effective: the drugs have many side-effects and are not curative, pudendal nerve block temporarily relieves symptoms, and neuromodulation involves the permanent positioning of an electric stimulator. At present, only few articles with a limited number of cases have been published:a multicenter Italian study showed a significant improvement of VAS and quality of life with sacral nerve stimulation in 11/12 patients with chronic idiopathic anal pain after a mean follow-up of 15 months [6]. Surgical decompression is not an easy technique, with possible serious complications and only few centers worldwide have accumulated sufficient experience.

Human adipose-derived stem cells (ASC) from processed lipoaspirates, injected with the lipostructure Coleman's technique [7], or isolated, cultured and reimplanted have been successfully used in many clinical trials for a number of clinical conditions [8]. We prospectively evaluate the feasibility of a new application of the lipofilling technique, based on multiple transperineal injections of autologous adipose tissue with stem cells in patients with pudendal neuralgia. Preliminary results on safety and effectiveness are reported, with the short-term incidence of pain recurrence as primary outcome measure.

Materials and Methods

Study Population and Inclusion Criteria

Patients were recruited from our outpatient clinic, from January 2011 to September 2012 and selected according to the following protocol:

1. Clinical diagnosis of pudendal neuralgia with presence of all Nantes essential criteria and at least one complementary sign;
2. Failure of 3 months medical therapy, based on 150 mg/day Pregabalin (Lyrica®, Pfizer Ltd, Latina, Italy) and 30 mg/day ketorolac tromethamine (Toradol®, Recordati s.p.a., Milan. Italy);
3. Evaluation of VAS score and quality of life, using the SF36 Health Survey [9] (registered trademark of Medical Outcomes Trust Inc., 275 Wyman Street , Suite 120, Waltham, MA 02451). This questionnaire comprises a multi-item scale, consisting of 36 questions, assessing eight health concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well being);
4. Preoperative PNTML with St Mark's electrode (Mediwatch UK Ltd., Rugby, UK), using the original technique, described in 1984 by Kiff and Swash [10]. Square valve stimuli of 0.1 msec duration were applied at 1-second intervals as the stimulating tip was positioned over the pudendal nerve. Normal values of pudendal nerve latencies in normal individuals were considered 2 ± 0.2 msec [5];
5. The psychologic state of patients was evaluated by a psychiatrist, as independent observer.

Presence of anal fissure, perineal abscess, solitary rectal ulcer, inflammatory bowel disease, prostatitis, pelvic endometriosis, anismus, neurologic diseases, and psychiatric disorders were exclusion criteria, while patients submitted to previous anorectal, urological, or gynaecological surgery were eligible for the study.

The ethics committee of the I.R.C.C.S. Ca' Granda, Ospedale Maggiore Policlinico of Milan, approved the study protocol. All patients gave written informed consent. All patients were all operated by the same surgical team, using the technique described below, without modifications.

Lipofilling Technique

Preoperatively, whole-bowel washing was performed and the patient received routine antibiotic prophylaxis, with a single shot of cefotaxime 2 g at the time of surgery. All patients were operated in the lithotomy position. We used the original Coleman's technique, based on three stages: fat harvesting, purification of lipoaspirate with centrifugation, and infiltration in the site of treatment [7], Fat donor sites were lower abdomen, flank, thighs, knee, and gluteal region. After tumescent injection of 0.5% lidocaine plus 1/500,000 epinefrine, a liposuction 3 mm atraumatic cannula (Bontempi Bmed srl, S. Giovanni in Marignano, Italy) connected with 20 mL syringe with a Luer-lock connector was introduced in the subcutaneous space and moved, to mobilize the fat tissue and facilitate its aspiration into the syringe, The lipoaspirate was centrifuged at 3,000 rpm for 3 minutes. The superior and inferior layers of the centrifuged sample were eliminated and then the middle layer with vital adipose cells was aspirated in a 10 mL syringe connected with a 2 mm atraumatic cannula for

infiltration (Bontempi Bmed srl, S. Giovanni in Marignano, Italy) and injected.

The infiltration technique was similar to the transperineal pudendal block: the ischial tuberosity was identified by palpation, the index finger of nondominant hand of the operator was inserted into the rectum to identify the ischial spine and to help guide for the needle. In case of unilateral neuralgia, each patient received four injections of about 2 mL of adipose tissue; in pts with bilateral neuralgia the injections were eight, with about 1.5 mL of lipoaspirate: four in the right and four in the left Alcock's canal. The first injection was nearby the ischiatic spine and the other three at a distance of about 5 mm along the Alcock's canal under the finger guidance. Acetaminophen plus codeine 500 mg tablets (Coefferalgan®,UPSA Medica, Milan, Italy) were available for postoperative pain control, when VAS was greater than 4.

Outcome Measures

We considered the incidence of recurrent pudendal neuralgia (VAS >5) at clinical examination as the primary outcome measurement. A nurse as independent observer administered VAS and SF-36. VAS was collected at 7 and 14 days and 1, 3, 6, 12 months after the operation; each patient was recalled at the right time after her/his date of surgery. SF-36 was scheduled at 3, 6, and 12 months. PNTML was repeated 12 months after the treatment. Patients who did not strictly follow the pre and/or postoperative protocol were excluded from the study.

Statistical Analysis

Continuous data are shown as mean (SD), and qualitative data as absolute frequencies and percentages. Data were analyzed with the statistical software package SPSS 16.0 for Windows XP® (SPSS Inc., Chicago, IL) was used. Preoperative and postoperative data were compared using a repeated measure variance analysis test for VAS and SF 36. PNTML data were analyzed by paired Student's *t*-test. Differences were considered significant at $P<0.05$.

Results

Preoperative Data

Out of 20 patients with pudendal neuralgia observed from January 2011 to September 2012, five were not eligible for the study: one for an anal fissure, one for pelvic endometriosis, one for prostatitis, and two for the coexistence of a psychiatric disorders. The other 15 (14 women, median age 60 ± 7 years, range 48–69) were enrolled: eight of them have had previous pelvic floor surgery (5 haemorrhoidectomy, 2 hysterectomy, 1 colpoperineorrhaphy), two had undergone a pelvic trauma, and one was a competitive cyclist. For the remaining four patients, the cause of pudendal neuralgia was unknown. Mean BMI was 24.7 ± 2.4 and no comorbidities were observed. All patients had symptoms of distal neuralgia affecting the rectal branch of the pudendal nerve; five patients had associated pain to vagina and perineum. In 11/15 patients (73.3%) pain was unilateral, bilateral in the others. Multiple vaginal parity was observed in 9/14 patients (64.3%), with a mean (SD) of parity of 2.1 (0.4). These patients had been suffering pain for a mean (SD) length of time of 59 (13) months.

Table 1 VAS in preoperative evaluation and during 12-month follow-up in 10 patients with pudendal neuralgia submitted to pudendal nerve lipofilling

Time	VAS (mean $\pm$ SD)	MSE
Preoperative	8.1 ± 0.9	0.27
7 days	7.1 ± 0.6	0.18
14 days	6.3 ± 0.5	0.15
1 month	5.3 ± 0.5	0.15
3 months	3.1 ± 0.6	0.18
6 months	2.6 ± 0.7	0.22
12 months	3.2 ± 0.6	0.20

* MSE = mean standard error.
A repeated measure variance analysis was used. F was 110.07, with $P<0.0001$.

In 6 months before recruitment, two patients had undergone biofeedback, and three had received local anaesthetic injection, 1.5 cm medial to the tip of ischial spine, using bupivacaine 0.25% (Recordati Industria Chimica Farmaceutica S.p.A., Milan, Italy) 6 mL and triamcinolone acetonide 40 mg/mL (Kenacort A Retard®, Bristol Myers Squibb s.r.l, Roma, Italy) 3 mL, under fluoroscopic guidance, with temporary (<2 months) relief of symptoms.

None of the patients suffered from psychiatric disorders, even though a medium level of anxiety, with a mean (SD) STAI X1 score of 44 (11.5) was observed. No one was treated with antidepressant drugs, while five had taken benzodiazepines for anxiety in the past. Tables 1 and 2 report the preoperative VAS score and SF36, respectively. Unilateral prolongation of latency was seen in 11 patients, while the others had bilateral prolongation, with a mean (SD) value of 2.75 (0.03) msec.

Operative Data

Mean operating time was 91.5 (10.1) minutes. Quantity of lipoaspirate was 19.7 (0.52) mL and two or three fat donor sites were chosen for each patient, namely lower abdomen in 15/15 patients, knee in 10, flank in 5, and gluteal region in 2/15. There was no operative mortality, or complications. All patients were discharged during

Table 2 SF36 Health Survey questionnaire in preoperative evaluation and during 12 –month follow-up in 10 patients with pudendal neuralgia submitted to pudendal nerve lipofilling (data expressed as mean ± SD)

Finding	Preoperative n = 10	3 months n = 10	6 months n = 10	12 months n = 10
Limitations: physical activities	15.5 ± 3.3	13.4 ± 2.0	10.7 ± 1.7	11.3 ± 1.8
Limitations: social activities for physical, or emotional problems	4.8 ± 0.6	5.1 ± 0.7	6.5 ± 0.6	6.4 ± 0.7
Limitations: usual role activities for physical problems	6.2 ± 1.3	6.4 ± 1.5	7.9 ± 1.5	7.8 ± 1.4
Bodily pain	5.1 ± 1.0	3.7 ± 0.6	1.0 ± 0.3	1.7 ± 0.4
General mental health	5.4 ± 1.2	4.9 ± 0.9	3.3 ± 0.6	3.4 ± 0.8
Limitations:usual role activities for emotional problems	4.4 ± 0.7	5.1 ± 0.8	5.9 ± 1.3	5.8 ± 1.2
Vitality	32.2 ± 4.4	31.0 ± 4.0	29.0 ± 3.7	29.6 ± 3.8
General health perceptions	11.4 ± 2.2	10.6 ± 2.1	9.3 ± 1.9	9.5 ± 2.0
Total	85.0 ± 4.5	80.2 ± 3.9	73.6 ± 3.7	75.5± 4.1

* A repeated measure variance analysis was used. F was 15.99, with $P < 0.0001$.

the first postoperative day. No patients needed more than Acetaminophen 1,000 mg/day plus codein 60 mg/day for pain control during the hospital stay.

Follow-up Data

Two patients had no improvement of pain and continued to use analgesic drugs. Three patients were lost during follow-up. Ten patients were free of pain within 12 months after the procedure with VAS > 5.

As shown in Table 1 pain significantly decreased (VAS 3.2 ± 0.6 vs 8.1 ± 0.9 in preoperative evaluation, $P < 0.001$): pain reduction was progressive until 6 months after the operation, while a slight reversal of the trend was observed 12 months after the operation, characterized by a mild worsening of the pain, which, however, remained significantly lower than at preoperative evaluation.

As shown in Table 2, quality of life significantly improved (from 85 ± 4.5 to 75.5 ± 4.1, $P < 0.01$), and the trend was similar to the one observed for VAS. There was a nonsignificant trend toward a better nerve conduction at PNTML 12 months after the treatment (2.64 ± 0.04 vs 2.75 ± 0.03 preoperative, P = 0.06).

Discussion

Pudendal neuralgia is an infrequent condition and Literature on the argument is scanty, particularly regarding the best treatment. Most patients address social forums to share their experience in the hope of finding an effective solution.

The clinical diagnosis, based on the Nantes criteria, may be confirmed by neurophysiologic tests, with delayed conduction in pudendal nerves at PNTML, signs of denervation at anal EMG, and abnormal distal rectoanal excitatory reflex at anorectal manometry, even though all these tests are not considered essential to the diagnosis [5]. Many patients show a typical clinical pattern of pudendal neuralgia with normal or minimally alterated neurophysiologic data, to the point that one associated sign in the Nantes criteria is normal PNTML. EMG has a limited sensitivity and specificity in the diagnosis of pudendal nerve entrapment and cannot give information about the causes of the nerve lesion [11].

Our results suggest that PNTML is not useful in follow-up, particularly when preoperative latencies are minimally prolonged.

As found by other authors [12], previous pelvic surgery was a possible cause of pudendal neuropathy in more than 50% of our patients. Even if literature distinguishes organic, and functional pelvic pain syndromes, the coexistence of both conditions in the same patient is frequent and often it is difficult to identify the real cause of pain. The coexistence of perineal pain with hemorrhoids, rectal prolapse and rectocele, particularly in multiparous women >50 years old, might induce inexperienced surgeons to perform an operation, such as a stapled transanal rectal resection, with the risk of

worsening the pain and other complications. In addition, anxiety and depression causing personality disturbances may heavily contribute to the onset and /or the persistence and severity of symptoms [13]. The conclusion is that patients with pelvic pain syndromes should be referred to dedicated centers for an accurate diagnostic work-up and the choice of the best treatment.

Unfortunately none of the presently available treatments for pudendal neuralgia is totally safe, or effective. Medical therapy with nonsteroid antinflammatory drugs, oxycodone-acetaminophen, morphine sulphate, tricyclic antidepressants, or antiepileptic agents may prove helpful [14], as well as recently reported for palmitoylethanolamide [15]. Nevertheless, the positive effect of drugs is temporary and none of these chemicals is free of side-effects, particularly when used in association. Various techniques for pudendal block have been described in the last 25 years, starting from the infiltration in the ischio-rectal fossa of sustained-release corticosteroids, or local anesthetics with, or without CT guidance [16], to infiltrations of the nerve in proximity to the ischiatic spine under radioscopic guidance. Complications are rare and usually not severe, but less than 50% of patients respond successfully to nerve block and most of them complain of pain recurrence after only 1 year [17].

Results with pulsed radiofrequency [18], pudendal nerve neuromodulation [6], botulinum A toxin [19] are limited to few patients, or referred to particular conditions (i.e., severe muscle spasm for botulinum toxin) and nothing is known about long-term results. Pulsed radiofrequency is supposed to deliver an electromagnetic field, which improves the neuro-cellular function with minimal cellular damage: Rhame et al. successfully treated a patient with left pudendal neuralgia refractory to conservative treatments, by introducing a 22 gauge 4 mm radiofrequency needle 1.5 cm medial to the left ischial spine and stimulating at a frequency of 2 Hz and a pulse width of 20 msec for a duration of 120 seconds at 42°.

Surgical decompression of pudendal nerve may be performed by four different approaches: trans-perineal [20], transgluteal [21], trans ischio-rectal [22], and laparoscopic [23]. All normally involve the section of the sacrospinal ligament, with the risk of rheumatologic problems, and possible lesion of the levator ani, or rectal nerves, particularly in the trans ischio-rectal approach. According to published data, about 30% of patients do not respond to surgery [24]. Furthermore only few surgeons have sufficient experience in this field and positive results are uncertain.

Multipotent ASC, first isolated in 2001 by Patricia Zuk from human processed lipoaspirates [25], can be cultured and expanded in vitro and possess the capacity to differentiate in osteoblast, adipocyte, chondrocyte, endothelial cell, myocyte, hepatocyte, pancreatic cell, and neuronal cell. ASC secrete various growth factors, particularly a platelet-derived and a basic fibroblast growth factor, both inducing angiogenesis and are able to suppress the immune and inflammatory response, by inhibiting the production of inflammatory cytokines and producing anti-inflammatory cytokines [8], More than 30 clinical trials on the use of adipose and /or ASC have already been published. Garcia-Olmo et al. [26] published several studies on the treatment of perianal and enterocutaneous fistulas in patients with, or without Crohn disease by injecting autologous ASC in the fistulous tract. They reported a healing rate greater than 70%. ASC have also been indicated as an effective therapy in restoring urinary and anal sphincter functions [27]: in 2010, Yamamoto et al. [28] successfully treated two patients with stress urinary incontinence by injection of ASC in the external urethral sphincter under endoscopic vision. Casabona et al. [29] used ASC, obtained with the Coleman technique, to treat lichen sclerosus of the vulva and other causes of vulvodinia with good results. Rigotti et al. used manual lipoaspirates to treat tissue damage after radiotherapy: in isolated stromal vascular fraction of 2 cc of human lipoaspirate, they found 1.07% of mesenchymal stem cell and at least 1.02×10^3 colony-forming units fibroblasts [30].

These experiences prompted us to apply the method also to pudendal neuralgia. Our study is an evaluation of preliminary results, mostly aimed at confirming the feasibility of the method. It surely has some limitations, particularly for the lack of a control group and the limited number of patients enrolled, but our results in terms of safety and efficacy are encouraging from the clinical point of view and deserve to be signaled. All our patients had previously undergone multiple and ineffective treatment attempts. It is well known that infiltration with local anaesthetics (with, or without steroids) may surely alleviate the pain, but their positive effect is always transitory: our patients experienced this before the lipofilling, the best result being a 2 months span free of pain. Our data with the lipofilling technique show only a moderate pain reduction during the immediate postoperative period (7–14 days), while after 3 months the reduction of pain is conspicuous. This pattern is opposite to the one normally observed after the anesthetic block, in which the immediate benefit obtained is lost after a short span. The delayed benefit of lipofilling seems to suggest a real efficacy of the procedure and an active role of the cellular implant rather than a honeymoon effect or a cushion effect given by the mechanical effect of the injection. As we only injected centrifuged ASC instead of cultured stem-cells, we cannot state whether the lipofilling technique in this application implies that injected vital adipose stem cells are able to differentiate into neuronal cells and repair the damaged nerve (which could explain the progressive reduction of pain subsequently observed) or whether the injection of adipocytes simply produces a “cushion” effect around the nerve. Experimental studies are mandatory to give a scientific answer to these questions.

Conclusions

In our experience, the pudendal nerve lipofilling turned out to be easy to perform, safe, and effective, with significant and persistent improvement of symptoms.

Furthermore, in the event of pain recurrence the procedure can be repeated. However, being a limited preliminary study our observation must be confirmed by more extensive experiences with longer follow-ups, and validated following case–control, or randomized studies.

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