

Laparoscopic Uterine Nerve Ethanol Neurolysis (LUNEN) in Patients with Chronic Pelvic Pain

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ABSTRACT

Objective: To investigate the efficacy of laparoscopic uterine nerve ethanol neurolysis (LUNEN) for pain management in patients with chronic pelvic pain (CPP).

Methods: LUNEN, as a chemical neurolysis procedure, was performed on 22 subjects, and these were compared with 20 controls that had a diagnostic laparoscopy alone. Pre-treatment and postoperative 6th month Visual Analogue Scale (VAS) scores were estimated and a subjective pain evaluation questioning patients' satisfaction about pain relief in the 6th month after surgery was also performed.

Results: A total of 31 (73.8%) out of 42 CPP patients had a laparoscopic pelvic pathology. Preoperative VAS scores were similar in the groups; however, the mean postoperative VAS score was significantly lower in the LUNEN group than in the control group (3.18 ± 2.88 vs. 5.35 ± 3.09; p=0.02). In the LUNEN group, the number of patients who stated that their pain was relieved partially or completely was also significantly higher than in the control group (82% vs. 40%, p=0.019).

Conclusion: LUNEN is a feasible, safe and effective surgical alternative to traditional surgical methods in patients suffering from CPP. *J Clin Exp Invest* 2016; 7 (1): 7-13

Key words: Chronic pelvic pain, uterine nerve neurolysis, laparoscopy, ethanol

Kronik Pelvik Ağrılı Hastalarda Laparoskopik Uterin Sinir Etanol Nörolizisi (LUNEN)

ÖZET

Amaç: Kronik pelvik ağrılı (KPA) hastalarda ağrı tedavisinde laparoskopik olarak uterin sinirin etanol ile nörolizisinin (LUNEN) etkinliğinin araştırılması

Yöntemler: Kimyasal bir nörolizis prosedürü olan LUNEN, 22 hastaya uygulandı ve bunlar sadece tanısalk laparoskopik yapılan 20 kontrol hastayla karşılaştırıldı. Tedavi öncesi ve tedavi sonrası altıncı ayda Vizüel Analog Skalası (VAS) değerlendirildi. Ayrıca, ağrı kontrolünde hasta memnuniyetini sorgulayan subjektif bir ağrı değerlendirmesi yapıldı.

Bulgular: 42 kronik KPA'lı hastadan 31'inde (%73,8) laparoskopik olarak pelvik patoloji izlendi. Gruplar arası preoperatif VAS skorları benzerdi. Ancak, postoperatif ortalama VAS skoru LUNEN grubunda anlamlı olarak daha azdı (3,18 ± 2,88 vs. 5,35 ± 3,09; p=0,02). Kontrol grubuna göre, kısmen veya tamamen ağrısının geçtiğini bildiren hasta sayısı LUNEN grubunda anlamlı olarak fazlaydı (%82 vs. %40, p=0.019).

Sonuç: LUNEN, kronik pelvik ağrıdan şikayetçi hastalarda uygun, güvenilir, etkili cerrahi bir yöntem olarak geleneksel cerrahi yöntemlere alternatiftir.

Anahtar kelime: Kronik pelvik ağrı, uterin sinir nörolizisi, laparoskopik, etanol

INTRODUCTION

Chronic pelvic pain (CPP), which is commonly described as continuous or intermittent pain in the lower abdomen lasting for at least 6 months, continues to be one of the most difficult and perplexing health condi-

tions [1,2]. It is also considered that this is a common clinical problem which accounts for as much as 25% of routine gynecological office visits and 20% of referrals to gynecology clinics [3,4]. CPP has a major impact on health-related quality of life, work productivity and health care utilization. Living with CPP may

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lead to anxiety, depression, sexual dysfunction and decreased quality of life (QoL) [5].

During the last few years, the development and the widespread use of endoscopic techniques make laparoscopy better procedure for patients with CPP. In fact, CPP is the indication for 40% of all gynecological laparoscopies in the United States [6]. The laparoscopic approach makes not only the detection but also the treatment of the underlying pathology of the pelvic pain feasible [6-9].

The nerve plexuses and parasympathetic ganglia in the uterosacral ligaments, which were first described in the last century [10], carry pain from the uterus and other pelvic structures to the brain. Pelvic pain syndromes are caused by several pathologies in relation to activation of nociceptors and transmission of signals in these pathways. Thus they are expected to respond to treatment of underlying disease or interruption of that transmission at any level. The surgical approach to the management of CPP is based on interruption of this transmission pathway, which can be achieved by transection of uterosacral ligaments. Although hysterectomy is an option for women who have completed their fertility; in women desiring future fertility or preservation of their uteruses, more conservative approaches are needed. Pelvic denervations, which consist of the interruption of cervical and uterine sensory nerve fibers, involve uterosacral ligament resection, also called laparoscopic uterine nerve ablation (LUNA), and presacral neurectomy (PSN). PSN is a surgical technique that can be performed only by surgeons who are highly experienced in retroperitoneal space surgery. This procedure requires not only a greater degree of surgical skill but also carries a higher risk of intra-operative complications and long-term consequences. On the contrary, LUNA is known as a simple, feasible, and therefore relatively commonly performed surgical procedure [11]. For instance, in the UK, about 50% of gynecological endoscopists perform LUNA routinely during the surgical treatment of endometriosis [12]. Complications reported due to LUNA include injuries of the ureter and the veins that lie just medial to the uterosacral ligament, and long-term consequences such as uterine prolapse and bladder dysfunction [11,13]. In fact, today, it is considered that both LUNA and PSN may have some important complications and thus more feasible methods are needed.

Chemical neurolysis destroys the microscopic neural architecture, and therefore interrupts the trans-

mission function of the nerves. The use of chemicals to destroy nerve cells for the treatment of pain has been used since the beginning of the 20th century. For this purpose, ethyl alcohol (ethanol) is a commonly used agent. Ethanol shows its effect by causing phospholipid, cerebroside and cholesterol output from the neuronal tissues and leading to lipoprotein and mucoprotein precipitation. It was first used as a neurolytic agent in 1902 in order to treat trigeminal neuralgia [14]. In 1933, Labat and Greene reported that injection of 33.3% alcohol can produce satisfactory analgesia [15]. Today, although chemical neurolysis techniques that use ethanol or other agents are frequently applied for the treatment of various pain syndromes and in order to block nerves and plexus in patients with cancer; there is no clinical study in the literature evaluating its role in the treatment of CPP. The aim of this study, therefore, is to investigate the efficacy of laparoscopic uterine nerve chemical neurolysis with the administration of ethanol as a neurodestructive agent in patients with CPP.

METHODS

A total of 42 women with persistent pelvic pain of at least 6 months' duration were consecutively enrolled; 22 of them comprising the laparoscopic uterine nerve ethanol neurolysis (LUNEN) group and 20 the control group. Laparoscopy followed by injection of ethanol to the uterosacral ligaments was performed in the study group. CPP patients selected as a control group underwent only laparoscopy without ethanol neurolysis. Subjects were blinded to the therapy methods that were administered. All patients were followed up for six months and preoperative and postoperative pain statuses were recorded.

An accurate history was recorded using the International Pelvic Pain Society (IPPS) form and a complete physical examination was performed. At admission, each woman underwent a gynecological pelvic examination and trans-vaginal ultrasound (TVUS). When non-gynecologic causes of CPP were suspected preoperatively, the patients selectively underwent gastroenterological, urological, orthopedic, and neurological examinations.

Patients with endometriomas, huge intramural myomas, large ovarian cysts and masses, pelvic organ prolapse, pelvic immobility with a fixed retroversion uterus and / or uterosacral or douglas nodularity and a suspicion of pelvic malignancy were excluded. Women under the age of 18 and over the age of 45 and those

in the postmenopausal period were excluded. Patients who had a history of hysterectomy or other pelvic surgery excluding cesarean section were also excluded.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. The subjects enrolled in the study were informed about the study and then, written informed consent was obtained by all of them. The Institutional Review Board (IRB) and Ethics Committee of our center approved the study protocol (14.2.2007-2007/1-16).

All surgical interventions were performed by the same surgical team. After induction of general anesthesia, the patient was placed in the low lithotomic position in order to perform pelvic laparoscopy. Immediately before surgery, each patient received a single dose of 1g IV of Cefazoline (Sefazol®, Mustafa Nevzat, Istanbul, Turkey) as a prophylactic antibiotic. A Foley catheter was inserted into the bladder. After executing a pneumoperitoneum with the use of a Verres needle, a 10-mm videolaparoscope was inserted umbilically, followed by the lateral insertion of two 5-mm ancillary trocars. After careful inspection of the pelvis to exclude organic diseases, the posterior leaf of the broad ligament was carefully inspected bilaterally to identify the course of the ureter. Uterosacral ligaments were also identified and grasped and elevated by an endoscopic grasper. A Verres needle was inserted midline halfway between the umbilicus and pubis and 5 ml 50% ethanol was slowly injected into each sacro-uterine ligament about 2 cm distally to the attachment of the ligaments to the cervix. After withdrawing the needle, hemostasis was controlled carefully and pelvic lavage was performed. Before completing the surgery,

patients underwent ablation/excision of endometriosis or lysis of adhesions if necessary. The women were allowed to eat and drink the evening after surgery and could ambulate as soon as they felt comfortable. All surgical interventions were performed as an outpatient procedure unless there was a surgical complication.

Severity of pain was estimated using a 10 cm visual analogue scale (VAS) ranging from “least possible pain” to “worst possible pain” and expressed as continuous numerical values [3]. The pain was arbitrarily considered severe in the event of a pain score with a value of 5 or more. The preoperative 7th day and postoperative 6th month VAS scores of the LUNEN group were compared with those of the control group. Additionally, a subjective pain evaluation by one of the study researchers was performed questioning patients’ satisfaction with pain relief in the 6th month after surgery.

Descriptive statistics were first generated with univariate analysis to determine the profile of the two groups. Bivariate analysis was performed using the Pearson chi-square test, Student’s t-test, and Mann-Whitney’s U-test as appropriate to compare mean values for parametric and nonparametric variables. For all statistical evaluations, the SPSS-14 (Statistical Package for Social Sciences version 14.0 for Windows) program (SPSS Inc., Chicago, IL) was used. Statistical significance was set at $P < 0.05$.

RESULTS

The characteristics of the subjects are reported in Table 1. No significant difference was detected between the two groups in age, BMI, or duration of CPP. Mean parity in the study and control groups was 3.0 ± 1.63 and 1.74 ± 1.24 respectively ($p=0.028$) (Table 1).

Table 1. Patient’s characteristics

| | LUNEN group (n=22) | Control group (n=20) | P |
|--|-----------------------|-------------------------|-------|
| Age (year) | 37.05±8.42 | 33.75 ±6.53 | 0.163 |
| BMI (kg/m ²) | 24.7±3.13 | 23.06±1.83 | 0.008 |
| Parity (no., mean ± SD) | 3.0±1.63 | 1.74 ±1.24 | 0.028 |
| Previous CS (n, %) | 5 (22.7%) | 4 (25%) | 0.640 |
| Duration of CPP (month) | 38.18±30.06 | 27.35±25.3 | 0.218 |
| Painful days per month (mean ± SD) | 24.7±3.13 | 23.06±1.83 | 0.152 |
| Number of previous hospital admissions (mean ± SD) | 4.27±2.52 | 3.65±1.89 | 0.370 |

LUNEN: Laparoscopic uterine nerve ethanol neurolysis, BMI: Body mass Index, CS: Cesarean section, CPP: Chronic pelvic pain, SD: Standard deviation

A total of 15 cases (68.2%) out of 22 patients in the LUNEN group had laparoscopically positive findings while there were 16 patients (80 %) with positive findings in the control group. The most common pa-

thology was adhesion (45.4%) in the LUNEN group; and endometriosis (40%) in the control group. The distribution of pelvic pathologies detected in diagnostic laparoscopy is listed in Table 2.

Table 2. Distribution of pelvic pathologies detected by laparoscopy

| | LUNEN group (n=22) | Control group (n=20) | Total |
|---------------------------------|-----------------------|-------------------------|-----------|
| Adhesion (n, %) | 9 (40.9) | 5 (25) | 14 (33.3) |
| Endometriosis (n, %) | 1 (4.5) | 4 (20) | 5 (11.9) |
| Ovarian Cyst (n, %) | 2 (9.1) | 2 (10) | 4 (9.5) |
| Pelvic Congestion (n, %) | 1 (4.5) | 0 (0) | 1 (2.4) |
| Uterine Fibroid (n, %) | 1 (4.5) | 1 (4.5) | 2 (4.8) |
| Ovarian cyst +Adhesion (n, %) | 1 (4.5) | 0 (0) | 1 (2.4) |
| Endometriosis + Adhesion (n, %) | 0 (0) | 2 (10) | 2 (4.8) |
| Endometriosis + Fibroid (n, %) | 0 (0) | 2 (10) | 2 (4.8) |
| No pathology (n, %) | 7 (31.8) | 4 (20) | 11 (26.2) |

LUNEN: Laparoscopic uterine nerve ethanol neurolysis

All patients who had adhesion (n = 17) underwent adhesiolysis; and in all patients diagnosed with endometriosis (n = 9), excision and cauterization of the implants were performed. Ovarian cystectomy was performed in five cases (in one the frozen section was studied and showed no malignancy). In all cases with fibroids, an intramural fibroid of less than 2 cm was present. In two patients whose fibroids were located close to the serosa, a myolysis with electrocautery was applied while no additional surgical procedure was performed on the other two patients whose fibroids were deep-seated. All except one of the laparoscopies were completed successfully, and one case was converted to laparotomy due to unsuccessful visualization. In one case, a trocar site hematoma followed by subsequent abscess developed. There was no postoperative bladder dysfunction. As postoperative treatment, two patients with a diagnosis of endometriosis received progesterone and one received GnRH analogue.

Mean preoperative VAS scores in the LUNEN and control groups were 7.59 ± 1.29 (range 6-10) and 7.90 ± 1.58 (range 5-10) respectively ($p=0.49$). After six months follow up the mean postoperative VAS scores were significantly lower in the LUNEN group than in the control group (3.18 ± 2.88 versus 5.35 ± 3.09 ; $p=0.02$) (Table 3).

When asked about subjective assessment of pain in the 6th month, six patients in the LUNEN group (27%) stated that pain had totally disappeared after

surgery, twelve (55%) stated that pain had lessened, and four (18%) stated that there had been no change in pain. In the control group, while only two patients (10%) stated that pain had completely disappeared, six (30%) stated that pain was reduced and twelve (60%) stated that there was no change in the pain ($p=0.019$) (Figure 1).

Table 3. Preoperative and postoperative VAS scores (mean \pm Standard deviation)

| | LUNEN group (n=22) | Control group (n=20) | p |
|--------------------------|-----------------------|-------------------------|------|
| Pre-operative VAS score | 7.59 ± 1.29 | 7.90 ± 1.58 | 0.49 |
| Post-operative VAS score | 3.18 ± 2.88 | 5.35 ± 3.09 | 0.02 |

LUNEN: Laparoscopic uterine nerve ethanol neurolysis, VAS: Visual Analog Scale

DISCUSSION

CPP is a problematic syndrome that is seen in approximately 15% of women of reproductive age, has a multifactorial and complex etiology involving psycho-social and biological factors, and is quite difficult to resolve [16]. Developments in noninvasive methods such as TVUS and invasive techniques such as laparoscopy provide us with some opportunities to reveal accompanying pathologies that could be a cause of pain in patients with CPP, but they do not always allow

us to solve the problem. In recent years, even though technological developments in endoscopy have made laparoscopy a useful method in the differential diagnosis and sometimes the surgical treatment of CPP, the negative laparoscopy finding rate has ranged from 8.2% to 63% [17-22]. In our study, 26.2% of the patients showed normal pelvic findings in laparoscopy (31.8% of the LUNEN group versus 20% of the control group). Although these were selected cases we found a relatively high rate of pelvic pathology corresponding to 73.8%. The two most common pelvic pathologies were adhesion (40.5%) and endometriosis (21.4%). Although our study population composed of only women without a history of pelvic surgery except for cesarean section, adhesion was still in the first place. In the literature, the most frequent coexistence is with adhesion, as well [23-26]. Kontoravdis et al. performed laparoscopy on 1629 patients with CPP and identified adhesion in 577 (35.4%) of them [23]. However, the mechanism of pain and the clinical benefit of adhesiolysis in pain relief are unclear in CPP patients with pelvic adhesion. While there is no consensus, location, vascularity, thickness, and size of adhesions and the extent of restriction of movements of organs caused by adhesions are considered the most important parameters involved in pain formation and its severity. We performed adhesiolysis in all cases of adhesion. A recent study has shown that in patients with CPP, treatment of concomitant adhesions (adhesiolysis) significantly improved six month postoperative VAS and QoL scores compared with the control group [25]. When it comes to endometriosis, this is known to be a pathology affecting approximately 10% of women of reproductive age. Generally, although the severity of pain is not well correlated with the severity of endometriosis (AFS stage), it is positively correlated with the total number of implants and with deep lesions especially with rectovaginal endometriosis [27]. Vercelli et al. were able to identify endometriosis in 32.5% of patients [18]. In this study, despite excluding fixed retroverted uterus, uterosacral and Douglas nodularity and endometrioma, we still found a high rate of endometriosis. Once again, these findings indirectly reveal the importance of endometriosis and pelvic adhesions in the etiology of CPP.

Although the management of CPP is challenging, treatment should be first directed at the underlying cause. However, due to the fact that its pathogenesis is complex, multifactorial and poorly understood, the pain can sometimes continue even though the apparent reason has been removed, and a non-specific

treatment is needed [2, 4, 5, 11, 12]. A recent meta-analysis showed that the improvement effect of medical treatments on pain and QoL is limited and many medical treatments also bring significant side effects in many patients [28]. Although there are several well-defined invasive approaches for the treatment of CPP in the literature, well-organized prospective randomized controlled studies are few [2, 11]. Traditionally, PSN and uterosacral resection techniques such as LUNA have been used to relieve pain in this group of patients, with differing success rates. Johnson et al. reported that LUNA was effective for dysmenorrhoea in the absence of endometriosis, although there was no evidence of the effectiveness of LUNA for non-dysmenorrhoeic CPP or for any type of CPP related to endometriosis [11]. While PSN is more effective than LUNA, this surgical technique can be applied only by experienced surgeons who familiar with the anatomy of the retro-peritoneum, because skill is required in addition to the presence of a significant degree of operative risk. The surgical procedure is more complex and the operation time is also longer in PSN. For these reasons, LUNA is currently a preferable process [2, 6, 11, 12]. While in surgical procedures the nerves are either cut or excised to interrupt the neural input, in neurolysis their microscopic neural architecture is chemically destroyed to interrupt the neural input [7, 14, 15, 29, 30, 31, 32]. In gynecological practice generally, neurolytic blocks are used in cancer-related CPP and in the form of percutaneous neurolytic superior hypogastric plexus block [29]. Chemical neurolysis of the superior hypogastric plexus has occasionally been performed for non-cancer pelvic pain. Pollitt et al. presented a woman with endometriosis-related severe CPP, who was successfully treated with chemical neurolysis of the superior hypogastric plexus [30]. As for uterine nerve chemical neurolysis on the other hand, only one case of uterine nerve ethanol neurolysis, published by Walid and Heaton, has been reported. In this paper, the authors reported the successful treatment of a case of pelvic pain caused by trigger points in the uterosacral stumps, using alcohol neurolysis. They highlighted the risk of voiding dysfunction after the procedure and recommended a two-step approach with an interval of two to three months [31]. In our series, ethanol at 50% concentration and total dose of 10 ml was used, and procedures were performed in one step. No problem directly associated with the neurolysis procedure was observed; including urinary or other local complications or systemic toxicity. In the literature on chemical neurolysis (intrathecal neuroly-

sis, sympathetic blockade, celiac plexus blockade and chemical hypophysectomy, etc.) alcohol is generally used in concentrations of 50% to 100%. Around 99% of the absorbed ethanol is rapidly metabolized by the liver enzymes, so in limited doses a systemic effect is not expected and alcohol neurolysis is generally seen as a safe procedure [32].

This study has several limitations. First, the sample size was relatively small, with a limited number of patients in both the study and control groups. Second, there was a lack of randomization of the groups. Third, our follow up time was also short and we were not able to have a reason to evaluate long-term pain outcomes of this method. Furthermore, the possible influence on QoL and psychosocial and sexual functions were not evaluated. Due to the surgical treatment of accompanying heterogeneous pelvic pathologies such as adhesion, endometriosis, fibroids and ovarian cysts, the conclusions drawn from this study are difficult for us to attribute to the results of ethanol neurolysis alone. Finally, some patients, especially those with severe endometriosis, received postoperative GnRH analogue or progesterone which could reduce the mean pain scores in this group of patients. Despite this, our study also has strength aspects. First of all, this is the first and only study evaluating the influence of LUNEN on pain scores in women with CPP. Second, this was a controlled study design. Additionally, as well as an objective assessment of pain with VAS, we also made a subjective evaluation by questioning the patients' satisfaction relative to the pre-treatment pain condition.

In conclusion, this study once again confirmed the importance of diagnostic laparoscopy in patients with CPP by showing a concomitant pelvic pathology in most cases. In patients suffering CPP; LUNEN, in combination with a specific treatment for underlying or concomitant pelvic pathology if present, is a simple, cheap, safe, and effective procedure that can be practiced by all gynecological laparoscopists. We consider it to be a very attractive procedure because of its potential simplicity and effectiveness. Nevertheless, large prospective randomized controlled studies are needed comparing LUNEN with other conservative methods, and especially with LUNA.

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