

Risk of recurrent menorrhagia after hydrothermoablation: role of GnRH analogues neoadjuvant treatment in long term successful rate

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Summary

Objective: to evaluate the long term effectiveness of presurgical therapy with GnRH analogues in patients who underwent hydrothermal endometrial ablation (HTA) for menorrhagia and assess the relationship between sonographically measured myometrium thickness and pelvic pain. **Materials and Methods:** A prospective randomized control study comparing 15 women (Group A) with presurgical subcutaneous triptorelin depot injection before HTA with controls (Group B, n=15). Inclusion criteria were: recurrent menorrhagia, uterus length < 12 cm, no previous hormonal therapy for at least six month, and family plan completed. Student's *t* test was applied, as appropriate, to compare continuous variables. Proportion were compared with chi-squared. **Results:** After 12 months of follow-up, Group A showed a significantly lower (0% vs 20%; *p* = 0.03) failure rate after hydrothermoablation than the Group B and a generally higher successful rate at 24 and 48 months. The discomfort, evaluated with VAS, showed a mean value of 47.6 ± 15.9 (\pm SD); 96.7% of women reported a mild-moderate postoperative pain. No perioperative and late complications were recorded. **Conclusions:** Presurgical treatment with GnRH analogues seems to improve long term efficacy of HTA. Perioperative pelvic pain seems to not be affected by myometrium thickness.

Key words: Menorrhagia; Hydrothermoablation; GnRH analogues.

Introduction

The prevalence of heavy menstrual bleeding interests about 65% of women during perimenopausal period [1].

The first thing that has to be excluded in the management of vaginal bleeding is endometrial cancer, that could be ruled out by hysteroscopy and endometrial biopsy [2, 3]. The hysteroscopic evaluation also allows to diagnose organic lesions such as polyps or submucosal myomas that can be removed with excellent results [3, 4]. Dysfunctional uterine bleeding (DUB) refers to unspecified bleeding from the uterus that occurs in the absence of any recognizable pelvic pathology. It affects about 30% [5] of women and can be treated with medical therapy or with surgery; however, some women do not accept hormonal treatment for contraindications or for intolerance. Moreover, in case of failure of medical therapy many, women are referred towards hysterectomy, which, although it can be performed in a minimally invasive way, remains a major surgical intervention [6]. Transcervical endometrial resection was introduced by Neuwirth in 1976 as a conservative surgical treatment and it is still now effective for the control of recurrent menorrhagia, with a success rate of 75-80% at five years and only 10-12% of failure managed with subsequent hysterectomy [7-11]. Hysteroscopic endometrial resection is a valid technique in a skilled surgeon's hand, but it requires a long learning curve

and it could have some side effects and even serious complications such haemorrhage or metabolic effects [12]. The second generation ablation techniques were introduced at the end of the 1990s; they were implemented with the aim to reduce the difficulties of the resectoscopic technique, hence to increase the diffusion of these less invasive procedures. The main purpose of these procedures is to reduce hysterectomies for abnormal uterine bleeding in an anatomically normal uterus [13, 14]. Hydrothermoablation is a simple procedure which uses a hysteroscope in a specific sheath introduced in the cervix; the uterine cavity is filled with saline solution at 90°C [15].

The aim of the present study was to evaluate the long term efficacy of presurgical treatment with GnRH analogues on the success rate of hydrothermal endometrial ablation (HTA) in the treatment for menorrhagia, and the relationship between myometrial thickness and pelvic pain.

Materials and Methods

Thirty premenopausal women with menorrhagia (abnormal uterine bleeding refractory to medical management) were enrolled in a longitudinal prospective clinical trial in the Department of Women's and Children's Health, Obstetrics and Gynecology Clinic, University of Padua (Italy).

An informed consent was obtained from all patients, which explained the involved side effects, risks, and benefits of medications and the procedures.

The patients were divided in 2 groups (A and B) on the basis of their arrival to the present Day Hospital ambulatory, in a ratio 1:1.

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Group A included 15 women which received subcutaneous triptorelin depot injection, (3.75 mg every 28 days for two times) [12]; the subsequent HTA was performed after 15-20 days from the last injection. Group B (control group) included 15 women and the HTA was performed in the proliferate phase, at days 7-10 of the menstrual cycle.

Inclusion criteria were: recurrent menorrhagia, uterus length < 12 cm, no previous hormonal therapy for at least six months, and completed family plan.

All women underwent presurgical evaluation with physical examination, office hysteroscopy and endometrial biopsy, Pap smear, and transvaginal ultrasound for excluding endometrial and cervical cancer.

Other exclusion criteria were desire for preservation of fertility, suspected genital tract infection or malignancy and previous endometrial ablation, submucous myoma larger than three cm or intramural myoma \geq five cm in the largest diameters, structural uterine anomalies, and adnexal pathologies.

At the presurgical transvaginal ultrasound, the authors also measured the anterior and the posterior uterine wall thickness, taking the size at the middle of the longitudinal scan in absence of myoma, and distinguished the measurement in \leq 25 mm, 26-30 mm, and \geq 31 mm.

Surgical procedure

HTA procedure consisted of cervical dilatation with Hegar dilator up to 7.5 mm; then a 2.9 mm fiberscope (0°) was introduced in an insulated hysteroscopic sheath. Its control mechanism was housed in a compact console mounted on a mobile cart. Circulation of fluid (0.9 % saline solution) was controlled by gravity, based on the height of the fluid container above the patients uterus, with actual intrauterine pressure reduced from hydrostatic pressure by the effect of the evacuation pump that recirculates fluid to the elevated reservoir. Only then the heating of circulating saline began, with a therapy cycle of ten minutes.

On completion of the therapy cycle, the operator was prompted to wait for one minute refreshing cycle to finish. As a safety feature, the HTA system was calibrated to detect loss of as little as ten ml of saline from closed loop circulation. The intrauterine pressure was determined by a microprocessor within 50-55 mmHg; over this value the passage of the saline solution through the salpinx may happen [15]. Four hours after the procedure, the authors evaluated the subjective symptoms as pelvic pain, cystitis, objective symptoms as vaginal and vulvoperineal burns, and the necessity of painkiller medicine.

The discomfort was assessed with visual analog scale (VAS) using this score: 0 as no pain and 100 the most painful. The pelvic pain was considered as mild from 0 to 40; moderate from 41 to 70, and severe from 71 to 100. These results were related to the measurement of the anterior and the posterior uterine wall thickness assessed at the presurgical transvaginal ultrasound.

All the women have been evaluated seven days after the procedure with a questionnaire by a telephonic interview asking the presence of foul smelling vaginal discharges, pelvic pain, fever, and urinary tract infections. An improvement of the menorrhagia as eumenorrhea, hypomenorrhea, and amenorrhea were considered a success of the procedure. The persistence of menorrhagia was considered a failure.

The follow up was conducted at 12, 24, and 48 months with a questionnaire including a validated postoperative menorrhagia questionnaire. The patients were asked about their perception of menstrual blood loss before and after surgery.

Statistical analysis was performed SPSS Statistics for Windows, Version 21.0. Results were expressed in absolute number and percentage for categorical variables, mean, and standard deviation for

continuous variables. Categorical variables were compared using the Chi-square test or Fisher's exact test when necessary. Continuous variables were compared using the Mann-Whitney U test. The level of significance was set at $p < 0.05$.

Results

The mean age of patients was 46.5 ± 4.7 years; 29 were multiparous and one was nulliparous.

Eighteen women had systemic disease (heart disease: nine, connective disease: nine); five were dyscoagulopathic and one had a previous pancreas transplantation. Dysfunctional endometrium was found in all 30 cases. No significant preoperative differences were observed between the two groups. Neoadjuvant treatment with GnRH analogues was well tolerated without any interruption for significant side effects, and only hot flushes and tachycardia were reported in seven and in two patients, respectively.

The procedure was completed in all 30 patients. Operative time, as measured from the initial introduction of the hysteroscope to its final removal was 16.0 ± 3.03 minutes). There were no serious intraoperative complications such as uterine perforation, hemorrhage or thermal injuries. In the postoperative time, only one patient had symptoms of cystitis, with a negative uroculture. No long term complications were observed; the telephone interviews after seven days confirmed no late complications.

In the Group A, at 12 months, the successful rate was 100% (ten eumenorrhea, one hypomenorrhea, four amenorrhea), at 24 months was 93.3% with nine eumenorrhea and five amenorrhea in Group A; in one patient there was a recurrent menorrhagia, but the patient did not need any further conservative or demolition surgical treatment. At 48 months the successful rate persisted at 93.3% with seven eumenorrhea, three hypomenorrhea, four amenorrhea; the same woman persisted in recurrent menorrhagia (Table 1) and underwent laparoscopic hysterectomy 39 months after endometrial ablation. No long term complications were referred and the satisfaction rate for the procedure was high in 80% of cases.

In Group B, at 12 months the success rate was 80% with seven eumenorrhea, two hypomenorrhea, three amenorrhea; in the remaining three cases there were recurrent menorrhagia after four, six, and eight months, respectively. At 24 months the success rate persisted in 80% with seven eumenorrhea, two hypomenorrhea, three amenorrhea; the failure persisted in three cases and one of these underwent a laparoscopic supracervical hysterectomy 14 months after the treatment. At 48 months the success rate decreased to 73.3 % with five eumenorrhea, six amenorrhea, two persistent menorrhagia, and another one recurred with menorrhagia after 36 months. None of these three patients recurred to other conservatives or demolition procedures (Table 1). No long term complications were referred; the satisfaction rate for the procedure was 67%.

Table 1. — *Triptorelin depot injection, 3.75 mg treatment (Group A) vs no treatment (Group B).*

Menstrual Status	12 months		<i>p</i>	24 months		<i>p</i>	48 months		<i>p</i>
	A (15)	B (15)		A (15)	B* (14)		A (15)	B* (14)	
Eumenorrhea (%)	10 (66.7)	7 (46.7)	0.1	9 (60)	7 (46.7)	0.3	7 (46.7)	5 (33.3)	0.3
Hypomenorrhea (%)	1 (6.7)	2 (13.3)	0.3	0	2 (13.3)	0.1	3 (20)	0	0.1
Amenorrhea (%)	4 (26.6)	3 (20)	0.3	5 (33.3)	3 (20)	0.2	4 (26.7)	6 (40)	0.2
Success (%)	15 (100)	12 (80)	0.03	14 (93.3)	12 (85.7)	0.3	14 (93.3)	11 (78.6)	0.1
Failure (%)	0	3 (20)	0.03	1 (6.7)	2 (14.3)	0.3	1 (6.7)	3 (21.4)	0.1

(*) One patient underwent laparoscopic supracervical hysterectomy at 14^o month from HTA.

Through statistical analysis, Group A with GnRH analogues neoadjuvant treatment showed a significant lower failure rate after hydrothermoablation than in Group B ($p = 0.03$; Table 1).

The discomfort, evaluated with VAS, showed a mean value of 47.6 ± 15.9 ; 13 patients had mild pain; 16 had moderate, and one had severe pain. In Group A there were six patients with mild pain, eight with moderate pain, and one with severe pain. In Group B there were seven women with mild pain and eight women with moderate pain. Only seven patients (one mild, five moderate, and one severe) needed painkiller therapy in postoperative time (ketorolac tromethamine ten mg i.v.). All the patients were discharged within eight hours after surgery.

There was no relationship between perioperative pelvic pain score and myometrial thickness (Table 2); no differences were observed between anterior or posterior wall myometrial thickness and pain score. Only one patient in Group A had severe pain, and an anterior and posterior wall uterine thickness of more than three cm was observed.

Discussion

Recurrent menorrhagia is the most common finding, frequently associated with a bad quality of life. Until 20 years ago, total hysterectomy was the option proposed for solving recurrent menorrhagia. In the last three decades recent developments in endoscopic technology have led to increase conservative and mini-invasive treatment of intrauterine lesions, including pre-neoplastic lesions, in women who require the preservation of the uterus [16, 17]. Also the conservative surgical treatment of DUB has made progress in recent years in the production of significantly modified endometrial ablation technology, with the introduction of the first and second generation ablation techniques.

Among first generation techniques the endometrial resection was the gold standard technique. The aim of this procedure is the excision or the destruction of endometrium and basal endometrial layer, thus preventing its future growth with progressive decrease in the menses at least over the first six months after the treatment [9]. Some authors demonstrated the long term efficacy of endometrial resec-

Table 2. — *Comparison between uterine wall thickness and postoperative pain.*

Group A: anterior uterine wall

Thickness uterine wall (mm)	Mild pain (0-40)	Moderate pain (41-70)	Severe pain (71-100)	<i>p</i>
≤ 25	6	6	-	0.7
26-30	-	2	-	0.1
≥ 31	-	-	1	1

Group B: anterior uterine wall

Thickness uterine wall (mm)	Mild pain (0-40)	Moderate pain (41-70)	Severe pain (71-100)	<i>p</i>
≤ 25	5	6	-	1
26-30	2	2	-	0.6
≥ 31	-	-	-	-

Group A: posterior uterine wall

Thickness uterine wall (mm)	Mild pain (0-40)	Moderate pain (41-70)	Severe pain (71-100)	<i>p</i>
≤ 25	6	6	-	0.7
26-30	-	1	-	1
≥ 31	-	1	1	0.5

Group B: posterior uterine wall

Thickness uterine wall (mm)	Mild pain (0-40)	Moderate pain (41-70)	Severe pain (71-100)	<i>p</i>
≤ 25	4	6	-	0.8
26-30	2	2	-	0.6
≥ 31	1	-	-	1

tion until eight years of follow up with higher efficacy with increasing age [8]. Endometrial transcervical resection requires a specific skill and needs a long learning curve; it could have a high rate of intraoperative complications such fluid overload syndrome with hyponatraemia, water intoxication, cerebral edema and cardiac overload, bowel or bladder thermal damage, and uterine perforation. To reduce or control the risks associated with the procedure, the use of spinal anesthesia to improve the outcomes in patients who remain awake has been proposed [18], but even if among the conservative procedures, endometrial resection remains the gold standard in skilled hands; it may aggravate the clinical condition of women with comorbidities.

To reduce the technical skill required to perform the endometrial resection, other new techniques, that include direct circulation of heated saline solution (hydrothermal ablation), microwave ablation, radiofrequency hyperthermia, and thermal balloon were created. These new ablation techniques require a simple instrumentation and their application is simple. These aspects are very important to reduce the rate of complications of the transcervical endometrial resection and to permit the diffusion of these techniques [12, 19]. These techniques are a good solution in the management of recurrent menorrhagia in high anaesthesiologic – surgical risk patients because they do not use hypotonic solution.

The thermal balloon endometrial ablation is performed by heating a fluid – filled balloon inside the uterine cavity and using both heat and pressure to destroy the endometrium [20]. The balloon is filled with saline solution heated at 82°C for eight minutes with an internal pressure of 170 mmHg. It produces a necrotic coagulation of the endometrium for indirect heat transfer from the balloon to the endometrium.

HTA is the only procedure which is performed under direct hysteroscopic vision [21–24]. The innovation of this technique consists in free circulation of saline solution at 90°C; this aspect permits the heat to spread within the entire uterine internal area, even the tubal ostia, with a myometrial deep thickness of one to three mm [23]. This procedure could be performed in presence of submucous myomas because the heated saline solution takes a coagulative effect also on irregular surface [25]. This is an important advantage, over many other endometrial ablation devices, which need a regular uterine cavity. During HTA procedure myoma's vessels are completely obliterated and sometimes the myoma could be reduced for necrosis.

Many studies carried out *in vitro* had analysed the cryothermic and hyperthermic effect on human myomas and the nearest myometrium. The myocell necrosis increases from 17% to 88% when these cells underwent an increase of the temperature from 45°C to 80°C for ten minutes. Instead the myocell necrosis increases from 12% to 27% when the temperature decreases from –20°C to –80°C. Moreover, the intrauterine pressure produces a compression on myoma's vessel with hypoxia and necrosis of the myoma [24].

The choice of these procedures is due to the necessity of the treatment of “difficult” patients for dyscoagulopathies, heart disease, autoimmune disease, and transplants; they are at high anaesthesiologic and surgical risk and cannot undergo dangerous surgical procedures (i.e. endometrial resection, hysterectomy).

Brun *et al.* have demonstrated an amenorrhea rate after six months of approximately 20% and 36% after 12 months from treatment with Cavaterm and an amenorrhea rate of 21% and 29% after six and 12 months with endometrial resection [26], whereas Hawe and Mettler in pilot studies

have obtained an amenorrhea rate of more than 50% but these results have not been confirmed in comparative trials [27–30].

The large reduction in menstrual blood loss after endometrial ablation results in a high satisfaction rate: 93% to 89% after Cavaterm and 80% to 79% after resection at six and 12 months of follow up, respectively [26].

The use of high temperature for ablation (80°C for the balloon and 90°C for HTA) forced many doctors to assess the cardiac effects, pelvic pain after endometrial ablation, the depth of the thermal damage on the uterus, and surrounding organs. In the procedure with balloon, they observed that the thermal damage was limited to the endometrium and the inner part of the myometrium [26].

After the treatment with balloon, some uteri were histopathologically examined after hysterectomy; the larger depth of myometrial damage (5.8 mm) was reached at the anterior wall at the hystmic portion. Instead in the nearest areas, excluding the uterine cornua where the wall thickness is very thin, the myometrial destruction occurred till 3.3 mm. The mean maximum depth of the myometrial damage in all the uterus was 3.4 ± 1.8 mm; in uterus treated for three times of 24 minutes at 81°C, the maximum depth of damage was 5.0 mm. This study showed that the depth of endomyometrial damage and the temperatures reached at uterine serosa permitted to perform the procedure safely and with low complication risks [23].

Among the second generation procedures, HTA is more versatile and it uses the coagulative effect of the hot saline solution on the endometrium and first layer of the myometrium. It has a good success rate with respect to the menorrhagia resolution and avoiding a hysterectomy. Moreover, it has the advantage of reducing the risks of fluid overload syndrome.

The present prospective randomised study on 30 patients let the authors to monitor the menstrual blood loss characteristics after the HTA treatment with a follow up of 12, 24, and 48 months. Among these patients, 15 were treated with GnRH analogues before surgery. The GnRH analogue neoadjuvant treatment aimed to reduce the endometrial vascularization and make an endometrial mucosa atrophy with better thermal destroying effect [26]. These effects induce a better visibility during the procedure and a less quantity of re-absorbed distension solution. The follow up at 12, 24, and 48 months highlighted how the patients pre treated with Triptorelin showed a better efficacy of the procedure rather than not treated patients, with a successful rate at 12 months of 100% vs 80%, and at 24 months of 93.3% vs 80%. At 48 months the global successful rate was 93.3% for Group A versus 73.3% of Group B. No difference with respect to intraoperative and long term complications of procedure were observed between the two groups. This is probably due to the action of Triptorelin on the endometrium and the first layers of the myometrium with a reduction of vessel number, and a decrease of the endometrial thickness and surface.

The analysis of the relationship between the thickness of the uterine wall and the postoperative pain highlighted the concept that there was no correlation between these two factors. A thick uterine wall seems not to protect during HTA, as well as a thinner wall does not expose to a risk of intensive pain. Likewise the thickness of the wall has no influence on the intensity and the length of perioperative pain.

The present results confirmed that endometrial ablation is an interesting alternative procedure to hysterectomy for menorrhagia, with a success rate of around 80-90%, and low patient's discomfort and hospital stay [31, 32].

Although it is well known that this technique could fail in 10-15% of cases just within 12 months, pre-surgical treatment with GnRH analogue seems to improve long term efficacy of HTA with a successful rate more than 90% at 48 months follow up. HTA is a simple surgical procedure with low complication rate and high acceptability of patients who preserve their psychophysical well being [33-35].

It is important to underline that the patient must have correct information and she has to decide the better treatment for herself. The most important thing is the high satisfaction rate of the women who maintain the integrity of their genital tract. The exclusion of patients who should be subject to other procedures [6, 36] and the correct selection of patients who undergo these procedures permit to obtain a high success rate at long term with an amenorrhea rate of 40%.

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