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CLINICAL ARTICLE

Randomized controlled trial of thermal balloon ablation versus vaginal hysterectomy for leiomyoma-induced heavy menstrual bleeding

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ABSTRACT

Objective: To compare the efficacy of thermal balloon ablation (TBA) with that of vaginal hysterectomy in the treatment of leiomyoma-induced heavy menstrual bleeding (HMB). **Methods:** An open-label randomized controlled trial was conducted between November 1, 2012, and October 31, 2014, in a tertiary care hospital in Delhi, India. Eligible women with HMB (aged ≥ 40 years, uterus size ≤ 14 weeks of pregnancy, leiomyoma ≤ 5 cm, uterocervical length ≤ 12 cm) were randomly assigned (1:1) to undergo TBA or vaginal hysterectomy using computer-generated random number tables. The primary outcome was the number of women in the TBA group with HMB 6 months after surgery. Analyses were by intention to treat. **Results:** Each group contained 20 women. No women in the TBA group had HMB at 6 months. Nineteen women were amenorrheic by 6 months and one was hypomenorrheic. **Conclusion:** TBA can replace vaginal hysterectomy in some perimenopausal women with uterine leiomyomas.

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1. Introduction

Heavy menstrual bleeding (HMB) accounts for 30% of all gynecologic visits, increases morbidity, reduces health-related quality of life, and has a substantial economic burden on the healthcare system [1]. One cause of HMB is uterine leiomyomas (or fibroids), which are common benign neoplasms found in 20%–77% of premenopausal women, of whom 20%–25% are symptomatic [2].

Vaginal hysterectomy is considered the gold standard in the treatment of leiomyomas. According to the National Centre for Health Statistics in the USA, vaginal hysterectomy is the second most commonly performed major surgery in women of reproductive age [3]. In 2010, 433 621 vaginal hysterectomies were performed in the USA, 45% of which were due to uterine leiomyomas [4]. In India, the vaginal hysterectomy rate among women of reproductive age is 7%–9%, with the most common indication being uterine leiomyomas [5,6]. Nevertheless, although vaginal hysterectomy provides definitive treatment, it is associated with the high risks of any major surgery. Therefore, recent focus in gynecologic practice has been to reduce rates of vaginal hysterectomy by using safer alternatives to minimize both morbidity and cost. Minimally invasive endometrial ablative procedures are fairly safe and

effective options, with quick return to daily activity and similar efficacies as vaginal hysterectomy [7].

Endometrial ablation aims to destroy the entire layer of endometrial tissue, including the deep basal glands, to successfully suppress menstruation. There are currently five endometrial ablation techniques that have been approved by the US Food and Drug Administration: thermal balloon ablation (TBA), circulating heated saline, bipolar radio-frequency, cryoablation, and microwave energy ablation [7]. TBA is effective in the treatment of HMB in premenopausal women with a normal uterine cavity who have no desire for future fertility and do not wish to undergo major surgery, or in women for whom surgery is contraindicated [8,9]. Amenorrhea rates following TBA range from 15% to 60%, with low retreatment rates and high patient satisfaction [7].

Previous studies have focused on the use of TBA for heavy bleeding in women with a normal-size uterus, yet its role in leiomyoma-induced HMB has been infrequently studied [3,7,10]. According to a 2013 Cochrane meta-analysis [11], TBA and endometrial resection are safe and effective alternatives to vaginal hysterectomy for HMB, with equivalent satisfaction rates; however, its role in leiomyoma treatment has not been addressed.

The aim of the present study was to compare outcomes of TBA for the treatment of HMB induced by uterine leiomyomas—e.g. reduction in menstrual bleeding, improvement in hemoglobin, operative events, and quality-of-life measures—with those of vaginal hysterectomy. Leiomyomas cause HMB by increasing the endometrial surface area, as well as vascularity and blood flow to the uterus [12]. Therefore, the

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hypothesis was that endometrial ablation in perimenopausal women with leiomyoma-induced HMB will ablate the basal endometrial layer, resulting in decreased menstrual flow or amenorrhea until menopause, after which leiomyomas are known to regress in size.

2. Materials and methods

An open-label, randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India between November 1, 2012, and October 31, 2014. Women older than 40 years who had no desire for future childbearing, HMB (pictorial blood loss assessment chart [PBAC] score ≥ 100), a uterine size up to that of 14 weeks of pregnancy, leiomyomas of 5 cm in diameter or less, and a uterocervical length of 12 cm or less were eligible for inclusion. Women with acute pelvic inflammatory disease or pelvic pathology (e.g. adenomyosis, gynecologic cancers [including endometrial malignancy], atypical endometrial hyperplasia, and submucosal leiomyomas) were excluded. Ethical clearance was obtained from the institutional ethics committee. All participants provided written informed consent.

Participants were randomly allocated into two groups (TBA and vaginal hysterectomy) in a 1:1 ratio using computer-generated random number tables. Participants, investigators, and data analysts were not masked to group assignment.

A detailed history was obtained from all participants. A physical examination was also performed, along with PBAC scoring. All requisite preoperative investigations were undertaken, including hemoglobin tests, cervical smear tests, ultrasonography, endometrial histologic examinations, and pre-anesthetic evaluation. The Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire was used to assess the quality of life before and after the procedures. The UFS-QOL consists of the symptom severity score (SSS) and the health-related quality of life (HR-QOL) score. SSS includes questions pertaining to severity of symptoms, and the HR-QOL score includes questions pertaining to concern, energy, activities, control, self-consciousness, and sexual functions [13]. The SSS and HR-QOL score were applied to formulas to obtain corresponding transformed scores indicating severity (Uterine Fibroid Symptom Transformed Score [UFS-TS]) and quality of life (Health-Related Transformed Score [HR-TS]), respectively, in terms of percentages.

Both TBA and vaginal hysterectomy were performed under spinal anesthesia in the postmenstrual phase of the cycle. TBA was performed using the LiNAMenotreat system (LiNA Medical, Glostrup, Denmark), which consists of a reusable Menotreat system controller and a single-use Menotreat balloon set with an inflatable silicon balloon catheter. Thorough curettage was performed to reduce the endometrial thickness before TBA. The balloon was inflated with normal saline at $85^{\circ}\text{C} \pm 3^{\circ}\text{C}$ with the pressure maintained at 200 ± 10 mm Hg for 11 minutes \pm 5 seconds. The maximal uterine cavity length for TBA was 12 cm as recommended by the manufacturer. Vaginal hysterectomy was performed using the standard technique.

Intraoperative variables—including blood loss, duration of surgery, need for blood transfusion, complications, and technical difficulty—were compared in both groups. Technical difficulty was assessed by asking the surgeon to grade the surgery as “easy,” “difficult,” or “very difficult.” Postoperative severity of pain was assessed using a visual analog scale (VAS) scored 4, 6, and 12 hours after surgery, and then on postoperative days 1 (24 hours), 2 (48 hours), and 3 (72 hours). For patients with early postoperative discharge (<72 hours), subsequent VAS scoring was performed by telephone. Duration of hospital stay, and early and late postoperative complications—including infection, fever, endometritis, pneumonia, thromboembolism, hematoma, cellulitis, and abscess formation—were noted and compared in both groups. The frequency of adverse events such as hematometra and postablation tubal sterilization syndrome was noted in women who underwent TBA.

Follow-up was performed at 1, 3, and 6 months after surgery to assess menstrual blood loss (PBAC score) in women in the TBA group and hemoglobin levels in both groups. Six months after surgery, improvement of symptoms and UFS-QOL scores (SSS and HR-QOL scores) was assessed in all women. Women in the TBA group were also assessed at 12 and 24 months after surgery for recurrence of HMB.

The primary outcome measure was the number of women with HMB in the TBA group 6 months after surgery for uterine leiomyomas. Secondary outcome measures were improvement in hemoglobin levels, intraoperative and postoperative events, and UFS-QOL scores in both groups.

A sample size of 40 was considered adequate assuming that 40% of women in the vaginal hysterectomy group and 8% in the TBA group would experience adverse effects (minor and major), and a reduction in the PBAC score of 342 in women undergoing TBA, with 80% power at a 5% level of significance [10,14]. Statistical analyses were by intention to treat and were performed using SPSS version 20.0 (IBM, Armonk, NY, USA). The χ^2 test was used to study baseline variables and symptoms; the unpaired *t* test was used to compare changes in UFS-QOL. The two-way repeated measures ANOVA test was applied for VAS scoring, and the McNemar test was used to compare symptom scores. *P* values and mean differences with 95% confidence intervals (CIs) were used to determine significance. $P < 0.05$ was considered significant.

3. Results

Twenty women were randomly assigned to each group (Fig. 1). None of the participants were lost to follow-up. The baseline characteristics of women in both groups were similar, other than uterocervical canal length (Table 1).

In terms of the primary outcome, no women in the TBA group had HMB at 6 months (Fig. 2). Eighteen (90%) women became amenorrheic after 1 month and continued to remain so until 6 months postoperatively. One of the other two women was hypomenorrheic (PBAC score 74) after 1 month and became amenorrheic after 6 months. The second woman in the TBA group had a PBAC score of 106 after 1 month and became hypomenorrheic by 6 months (PBAC score 80). At 12 months after TBA, 1 (5%) woman had a recurrence of HMB for which she underwent vaginal hysterectomy, 2 (10%) became hypomenorrheic, and 17 (85%) remained amenorrheic. At 24 months, of the 19 women in the TBA group who had not undergone vaginal hysterectomy, 15 (79%) remained amenorrheic and 4 (21%) had hypomenorrhea.

There was a significant increase in hemoglobin levels in both the TBA and vaginal hysterectomy groups after 6 months, rising from 108.8 g/L to 127.5 g/L and 101.9 g/L to 123.2 g/L, respectively ($P < 0.001$ for both). There was no significant difference between the two groups at 6 months ($P = 0.192$).

Operative time was significantly shorter in the TBA group than in the vaginal hysterectomy group ($P < 0.001$) (Table 2). Blood loss was also significantly lower in the TBA group ($P < 0.001$) (Table 2). The number

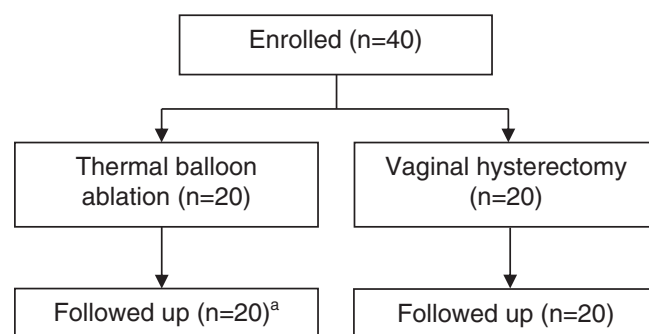


Fig. 1. Flow of patients through the study. ^a One woman underwent vaginal hysterectomy 12 months after thermal balloon ablation.

Table 1
Comparative demographic and clinical profile.^a

Variable	Thermal balloon ablation (n = 20)	Vaginal hysterectomy (n = 20)	P value
Age, y	44.25 ± 3.41 (40–50)	43.95 ± 1.95 (40–47)	0.736
Parity	2.85 ± 1.226 (1–7)	3.25 ± 1.20 (1–6)	0.305
Abortions (spontaneous and induced)	0.60 ± 0.68 (0–2)	0.9 ± 1.02 (0–3)	0.163
Body mass index ^b	26.63 ± 4.51 (20.0–36.57)	25.53 ± 3.52 (20–31.64)	0.395
Duration of menstrual flow, d	9.50 ± 4.14 (3–20)	9.90 ± 3.79 (6–20)	0.752
PBAC score	624.35 ± 280.12 (192–974)	668.25 ± 199.21 (300–965)	0.571
Duration of symptoms, y	1.73 ± 1.41 (0.25–5)	1.62 ± 1.15 (0.5–4)	0.460
Symptom severity score	27.35 ± 3.34 (23–37)	27.80 ± 2.60 (23–32)	0.638
UFS-TS, %	60.43 ± 10.45 (46.68–90.60)	61.85 ± 8.14 (46.87–75.00)	0.635
Health-related quality of life	102.90 ± 8.36 (80–114)	106.90 ± 5.27 (87–114)	0.080
HR-TS, %	36.26 ± 7.20 (26.72–56.03)	32.80 ± 4.54 (26.72–50)	0.079
Hemoglobin, g/L	108.80 ± 15.20 (82.0–146.0)	101.90 ± 13.90 (84.0–137.0)	0.144
Leiomyoma size, cm	2.74 ± 0.84	3.86 ± 0.94	0.719
No. of leiomyomas	1.35 ± 0.10 (1–2)	1.45 ± 0.60 (1–3)	0.188
Uterocervical canal length, cm	9.80 ± 1.47	9.90 ± 0.78	0.003
Endometrial thickness, mm	7.81 ± 3.09 (4–17.8)	8.31 ± 2.30 (4–15)	0.566

Abbreviations: PBAC, pictorial blood loss assessment chart; UFS-TS, Uterine Fibroid Symptom Transformed Score; HR-TS, health-related transformed score.

^a Values are given as mean ± SD (range) unless indicated otherwise.

^b Calculated as weight in kilograms divided by the square of height in meters.

of operations deemed technically easy was significantly higher in the TBA group than in the vaginal hysterectomy group ($P < 0.001$) (Table 2). No cervical lacerations, uterine perforations, vessel injuries, or injuries to viscera (enterotomy, ureteric injury, cystotomy) were noted in either group.

Postoperative pain score was significantly lower in the TBA group than in the vaginal hysterectomy group at all timepoints ($P < 0.001$) (Fig. 3). However, the pattern of the decrease in intensity of postoperative pain (VAS score) was similar in both groups ($P_{\text{interaction}} = 0.764$). The mean duration of hospital stay was significantly lower in the TBA group than in the vaginal hysterectomy group (36.65 vs 87.60 hours; $P < 0.001$; mean difference 50.9 hours, 95% CI 46.20–55.69). There were no early or late complications, such as urinary tract infections, fever, endometritis, pneumonia, thromboembolism, hematoma, or cardiorespiratory arrest, in either group.

After 6 months, there was a significant improvement from baseline in the number of patients affected by dysmenorrhea, pelvic pain, backache, high urinary frequency, and dyspareunia in the two groups (Table 3). The number of patients for whom symptoms of these problems had resolved by 6 months did not differ between groups (Table 3).

On evaluating the quality of life scores, UFS-TS reduced from 60.43% to 7.79% in the TBA group and from 61.85% to 2.02% in the vaginal hysterectomy group at 6 months after surgery (Fig. 4), with a difference in mean change of 7.18% (95% CI 1.29–13.07; $P = 0.018$). Mean increase in HR-TS was $58.17 \pm 9.06\%$ in the TBA group and $64.04 \pm 3.63\%$ in the vaginal hysterectomy group (Fig. 4), showing an improvement in

quality of life in both groups. The difference in mean change of was -5.87 (95% CI -10.29 to -1.45 ; $P = 0.011$).

4. Discussion

In the present study, all women who underwent TBA for leiomyoma-induced HMB achieved hypomenorrhea or amenorrhea at 6 months after surgery. Apart from one patient who underwent vaginal hysterectomy at 12 months, all women remained hypomenorrheic or amenorrheic at 24 months. Additionally, shorter operating times, less blood loss, decreased postoperative pain, and shorter hospital stays were recorded with TBA than with vaginal hysterectomy. Hemoglobin levels, the SSS, and the HR-QOL score improved in both groups at 6 months after surgery.

Several trials [9,14–17] have studied the efficacy of TBA in women with HMB and a normal-sized uterus, with success rates ranging from 83% to 91%. Nevertheless, studies comparing the efficacies of TBA and vaginal hysterectomy in women with uterine leiomyomas remain scarce.

Dickersin et al. [14] compared hysterectomy with roller ball ablation and TBA among women with a normal-sized uterus without any organic pathology, and found that endometrial ablation had an 84.9% efficacy in resolving dysfunctional uterine bleeding, compared with 94.4% for hysterectomy. Sesti et al. [18] performed a randomized study among women with HMB allocated to TBA or laparoscopic supracervical hysterectomy, and confirmed the effectiveness of TBA as a possible treatment for HMB. A Cochrane review [11] compared various endometrial destruction techniques with hysterectomy for HMB treatment among premenopausal women and concluded that endometrial resection and ablation are alternatives to hysterectomy because both

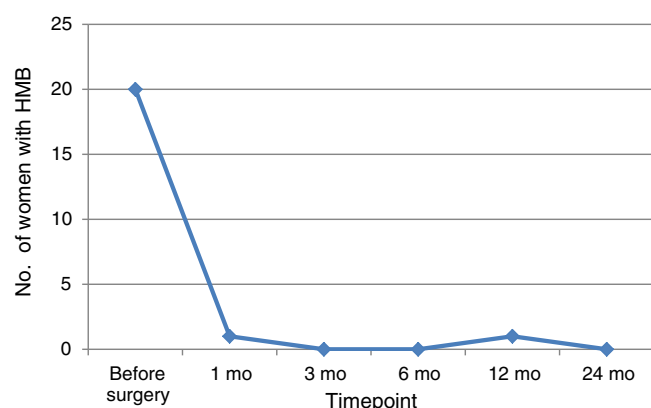


Fig. 2. Frequency of HMB after thermal balloon ablation. Abbreviation: HMB, heavy menstrual bleeding.

Table 2
Operative outcomes.^a

Intraoperative events	Thermal balloon ablation (n = 20)	Vaginal hysterectomy (n = 20)	P value
Operating time, minutes	21.60 ± 2.90	120.50 ± 16.92	<0.001
Blood loss, mL	21.50 ± 6.90	673.00 ± 212.63	<0.001
Blood transfusion	0	12 (60)	<0.001
Intraoperative complications	0	0	
Technical difficulty			<0.001
Easy	20 (100)	4 (20)	
Difficult	0	15 (75)	
Very difficult	0	1 (5)	

^a Values are given as mean ± standard deviation or number (percentage), unless indicated otherwise.

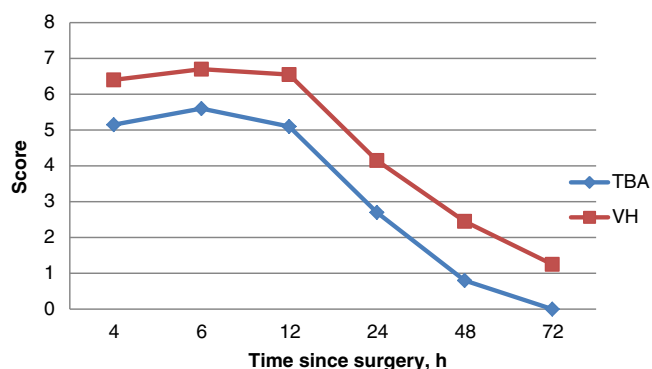


Fig. 3. Postoperative severity of pain assessed using a visual analog score. Scores of 1–3 indicate mild pain, 4–6 moderate pain, and >6 severe pain. Abbreviations: TBA, thermal balloon ablation; VH, vaginal hysterectomy.

procedures are effective and have high satisfaction rates. Nevertheless, although hysterectomy is associated with longer operating times, a longer recovery period, and higher rates of postoperative complications, it offers permanent relief from HMB [11].

Studies assessing the efficacy of TBA on leiomyoma-induced HMB remain scarce. A study by Soysal et al. [10] included women with leiomyomas of up to 5 cm and a uterocervical length of up to 12 cm, and compared TBA with roller ball ablation. The pretreatment PBAC was 384.3, and was reduced to 41.1 12 months after surgery ($P<0.001$) among women who underwent TBA, with an amenorrhea rate of 11.9%. In a study by Mettler [8], 50% of women with adenomyoma or leiomyomas who underwent TBA had hypomenorrhea and 50% underwent hysterectomy after ablation after 48 months of follow-up.

In the present study, TBA was highly efficacious: the amenorrhea rate among women who underwent TBA was 95% at 6 months, 85% at 12 months, and 79% at 24 months; and the hypomenorrhea rate was 5%, 10%, and 21% at 6, 12, and 24 months, respectively. After 12 months, one woman underwent vaginal hysterectomy. The higher rates of amenorrhea found in the present study than in previous studies could be attributed to the thorough curettage performed before the procedure to reduce endometrial thickness and ensure ablation of the basal layer. However, Soysal et al. [10] used gonadotropin-releasing hormone analog over 2 months for endometrial thinning, while Kim et al. [19] performed TBA without endometrial preparation.

Significant improvements in hemoglobin levels were observed in both groups in the present study, with the values being similar to those of Soysal et al. [10], who showed a mean hemoglobin improvement of 27 ± 19 g/L at 12 months of follow-up.

In the present study, women undergoing vaginal hysterectomy had a longer operating time (120 min) and more blood loss (673 mL),

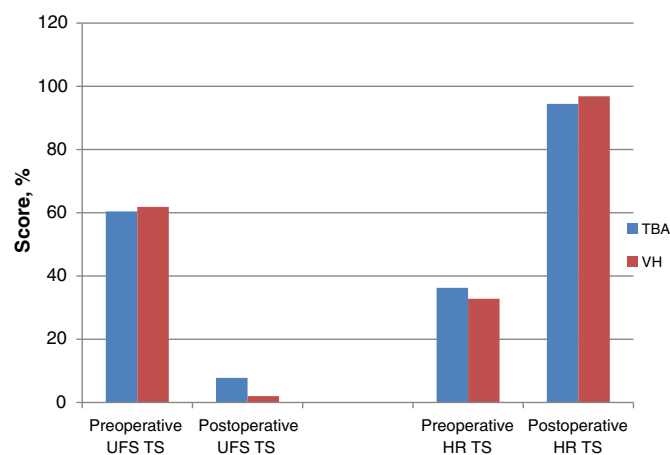


Fig. 4. Change in UFS-TS and HR-TS. Abbreviations: UFS-TS, Uterine Fibroid Symptom Transformed Score; HR-TS, Health-Related Transformed Score; TBA, thermal balloon ablation; VH, vaginal hysterectomy.

with 60% of women requiring a blood transfusion, than did women undergoing vaginal hysterectomy in a study by Bogani et al. [20] (operating time 85 minutes; blood loss 150 mL; blood transfusion 5%). It is noted, however, that all women who underwent vaginal hysterectomy in the present study had a uterine size of up to that of 14 weeks of pregnancy and volume reduction was performed either by enucleation or wedge resection. Bogani et al. [20] did not mention the size of the uterus nor the techniques used for volume reduction.

The present study showed similar postoperative pain patterns in both groups at all timepoints, but the pain score was significantly higher in the VH group. Soysal et al. [10] showed a linear pain score at 12 hours (3.1 ± 1.7) for both TBA and roller ball ablation, and a similar observation was made by Sesti et al. [18], who reported that postoperative pain intensity at 24 hours was significantly lower in women treated with TBA than in those who underwent laparoscopic supracervical hysterectomy. Lakeman et al. [21] compared the effects of electric bipolar vessel sealing and conventional suturing on postoperative pain and reported less pain on the evening after vessel sealing surgery (4.5 vs 5.7), with subsequent similar pain scores. In the present study, the conventional method of vaginal hysterectomy was used, with a postoperative pain score of 6.7 being observed on the evening of the surgery.

The present study showed longer hospital stay in both groups compared with previous studies. TBA in this study was performed under spinal anesthesia, whereas other studies used local anesthesia [14,22]. In the study by Dickersin et al. [14], 2.9% of women undergoing vaginal hysterectomy had a urinary tract infection, 10% had cuff cellulitis, 1.4% had pneumonia, 4.3% had cardiorespiratory arrest, and 2.9% had a thromboembolic event. Further, among women in the TBA group, 1.8% had a urinary tract infection and 1.8% had hematoma formation [14]. No early or late postoperative complications were noted in either group in the present study.

The current study evaluates symptom relief after TBA. Improvement of symptoms, including pelvic pain, backache, and dyspareunia, at 6 months after surgery in both groups reached statistical significance. The improvement seen in dysmenorrhea following TBA could be attributed to decreased synthesis of prostaglandins by the ablated endometrium, although such observations are yet to be reported in the literature.

A significant improvement in quality of life in both groups was observed in the present study. Soysal et al. [10] reported a 61% satisfaction rate in the TBA group. Dickersin et al. [14] showed that the hysterectomy group had a significantly greater reduction in pain ($P<0.001$) and fatigue ($P=0.02$) than the endometrial ablation group at 6 months of follow-up. Penezic et al. [23] reported an 87% patient satisfaction rate after TBA. Figure, 7–10 years after surgery (88% at 1–5 years), but hysterectomy rates were 2.4 times greater in the long-term follow-up period.

Table 3

Number of patients with resolution of symptoms after 6 months.^a

Symptoms	Thermal balloon ablation	Vaginal hysterectomy	P value ^b
Dysmenorrhea	16/16 (100)	19/19 (100)	>0.99
P value ^c	<0.001	<0.001	–
Pelvic pain	13/14 (93)	14/14 (100)	>0.99
P value ^c	<0.001	<0.001	–
Backache	10/16 (63)	9/16 (56)	>0.99
P value ^c	0.002	0.004	–
Increased urinary frequency	2/4 (50)	5/5 (100)	0.487
P value ^c	0.50	0.63	–
Dyspareunia	1/1 (100)	8/8 (100)	>0.99
P value ^c	>0.99	0.008	–

^a Values are given as number of women with resolved symptoms at 6 months/number of women who had symptoms before surgery (percentage).

^b Between-group comparison.

^c Comparison with baseline.

According to the latest evidence from the US Food and Drug Administration [24,25], there is a possibility of in situ undiagnosed uterine sarcoma after minimally invasive surgery (morcellation) for uterine leiomyomas. In the present study, pre-procedure endometrial biopsy sampling was performed for all women and was found to be normal. Additionally, during the follow-up period, there was no irregular or heavy bleeding, abdominal pain, or increase in uterine size (as assessed by pelvic examination), thus ruling out the possibility of uterine sarcoma left in situ. However, there are no previous studies focusing on uterine sarcoma after TBA.

The limitations of the present study include the small sample size and lack of assessment of reduction in total uterine volume after surgery.

To conclude, the present study compares TBA with vaginal hysterectomy in the treatment of leiomyoma-induced HMB and its associated symptoms. The efficacy of TBA was 100%, with 95% of women attaining amenorrhea, whereas 5% achieved hypomenorrhea at 6 months after surgery. TBA is an efficacious, technically simple, minimally invasive, and cost-effective alternative to hysterectomy in perimenopausal women with symptomatic leiomyomas. Carefully selected women could be offered TBA as first-line management.

Conflict of interest

The authors have no conflicts of interest.

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