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Original Article

A Randomized Controlled Multicenter US Food and Drug Administration Trial of the Safety and Efficacy of the Minerva Endometrial Ablation System: One-Year Follow-Up Results

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ABSTRACT **Study Objective:** To assess the safety and effectiveness of the Minerva Endometrial Ablation System for the treatment of heavy menstrual bleeding in premenopausal women.

Design: Multicenter, randomized, controlled, international study (Canadian Task Force classification I).

Setting: Thirteen academic and private medical centers.

Patients: Premenopausal women (n = 153) suffering from heavy menstrual bleeding (PALM-COEIN: E, O).

Intervention: Patients were treated using the Minerva Endometrial Ablation System or rollerball ablation.

Measurements and Main Results: At 1-year post-treatment, study success (alkaline hematin $\leq$80 mL) was observed in 93.1% of Minerva subjects and 80.4% of rollerball subjects with amenorrhea reported by 71.6% and 49% of subjects, respectively. The mean procedure times were 3.1 minutes for Minerva and 17.2 minutes for rollerball. There were no intraoperative adverse events and/or complications reported.

Conclusion: The results of this multicenter randomized controlled trial demonstrate that at the 12-month follow-up, the Minerva procedure produces statistically significantly higher rates of success, amenorrhea, and patient satisfaction as well as a shorter procedure time when compared with the historic criterion standard of rollerball ablation. Safety results were excellent and similar for both procedures. Journal of Minimally Invasive Gynecology (2017) 24, 124–132 © 2016 AAGL. All rights reserved.

Keywords: Endometrial ablation; Heavy menstrual bleeding; HMB; Hysteroscopy; Minerva endometrial ablation system; Rollerball

Since the early 1980s [1], endometrial ablation has become a successful treatment modality in the armamentarium for the management of patients with heavy menstrual bleeding (HMB; PALM-COEIN: E, O) who completed their childbearing. Endometrial ablation is currently used worldwide as a safe and less invasive alternative to hysterectomy. Utilization of resectoscopic endometrial ablation/resection modalities was and continues to be low because of the high degree of technical complexity, requirement for

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well-developed hand–eye–foot coordination, long learning curve, and the risks associated with the use of nonelectrolyte solutions for uterine distention [2,3]. In an attempt to rectify this persistent adoption problem, a number of nonresectoscopic devices were developed and approved by the US Food and Drug Administration (FDA). Using a randomized controlled trial (RCT) design for each pivotal trial, the effectiveness and safety of each method was shown to be "noninferior" when compared with rollerball endometrial ablation [4–13].

As a result, the use of endometrial ablation as a less invasive alternative to hysterectomy grew significantly [14]. However, the impact of adoption of these procedures on the overall number of hysterectomies in the United States is still unclear. Some reports indicate that the total number of (inpatient) hysterectomies performed annually declined to 433 621 cases in 2010 [15]. Other reports suggest the total number of inpatient and outpatient hysterectomies remained static, at approximately 600,000 cases a year [16]. Questions and concerns have been raised about high subsequent additional surgical reintervention rates, such as reablation and/or hysterectomy performed for recurrent HMB and/or new pelvic pain. These rates are reported to range between 16% and 24% [17–21].

The Minerva Endometrial Ablation System (Minerva Surgical, Inc., Redwood City, CA) was developed as an attempt to improve outcomes by using a novel technologic approach. Starting in 2015, the FDA adopted a new clinical trial design methodology, introducing the Objective Performance Criterion as the study control [22], which represents a composite of success rates for all previously FDA-approved nonresectoscopic endometrial ablation systems (ThermaChoice, NovaSure, Genesys HTA, Her Option, and MEA) as reported in their respective FDA trials. The Minerva Endometrial Ablation System is the first device to be evaluated and approved by the FDA using this new Objective Performance Criterion control [23]. Clinical results reported in this single-arm Objective Performance Criterion controlled study demonstrated that at the 12-month follow-up, the Minerva Endometrial Ablation System is safe and effective while producing results that were statistically significantly superior when compared with the Objective Performance Criterion control and published elsewhere [24]. This research effort had the goal of being a validator of previous clinical results [24] in a rigorous RCT environment.

Methods

This study was conducted under an FDA-approved Investigational Device Exemption (G110215) and was sponsored by Minerva Surgical, Inc. This investigation was a randomized, double-arm, multicenter, controlled, international study, with rollerball ablation serving as the control. The study was conducted at a total of 13 academic (n = 8) and private (n = 5) medical centers in the United States (n = 8), Canada (n = 4), and Mexico (n = 1) and in full compliance with the International Conference on Harmonization and Good Clinical Practices, including recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions, and standard ISO14155. In accordance with federal requirements and existing practices [25,26], study progress was monitored by a Data Safety Monitoring Board and a Clinical Events Committee.

Clinical Protocol

The primary objective of the study was to evaluate the safety and effectiveness of the Minerva Endometrial Ablation System (Test) as compared with hysteroscopic rollerball ablation (Control) in reducing menstrual blood loss as measured by the alkaline hematin (AH) method at 12 months post-treatment and the occurrence of any adverse events (AEs). Study success was defined as a reduction in menstrual bleeding from $\geq$160 mL pretreatment to $\leq$80 mL at 12 months post-treatment. Secondary objectives included amenorrhea rate and treatment parameters (procedure time, anesthesia type). Patient satisfaction was assessed using a patient survey and a validated Menstrual Impact Questionnaire [27].

The effect of ablation on premenstrual syndrome (PMS) symptoms was evaluated by collecting symptom data at baseline and at 12 months after the procedure. Subjects were also asked if they experienced dysmenorrhea. At baseline, the available answers were binary in nature (yes or no). To assess the impact of ablation on dysmenorrhea, subjects who answered yes were evaluated again at 12 months. If dysmenorrhea later developed in subjects who did not report it at baseline, data on such effects were collected and categorized as an AE.

Uterine sound and uterine cavity lengths, cervical dilation, and the position of the uterus were recorded. Investigators were required to rate the Minerva device with respect to general ease of use, device insertion, deployment, ability to seal the cervical canal, device removal, and overall user satisfaction.

All subjects qualifying for study participation and treatment were block randomized from a centralized electronic patient database in a 2:1 scheme to either the Test or Control Group. The subjects were further stratified by baseline age ($\leq$40 and >41 years). Endometrial pretreatment was not used in the Minerva randomized subjects, whereas wire loop resection of the endometrium was used as a mechanical means of endometrial pretreatment for subjects randomized to the rollerball arm of the study.

Clinical sites, investigators, and research staff were selected based on their qualifications and experience, including having significant experience in conducting clinical research, adequate facilities, and the ability to comply with all scientific, regulatory, and ethical site selection requirements. The main surgical prerequisite for study participation was significant experience in conducting resectoscopic surgery (rollerball ablation, endometrial resection, other). At the time of study initiation, study investigators had an average of 22.8 $\pm$ 3.6 years of experience in performing these procedures.

Statistical Methods

As required by the FDA, a formal Statistical Analysis Plan (SAP) was developed and approved before study initiation. The SAP outlined strict definitions and rules regarding safety and effectiveness analysis, subject accountability, missing data, and other procedures.

The study sample size was computed to yield at least 80% power to demonstrate noninferiority (noninferiority margin of 20%) of Minerva to rollerball, according to the approach described by Farrington and Manning [28]. Based on a 1-tailed test of proportions with α (Type 1 error) equal to .025, and success rates in the rollerball arm (Control) of 80% and in the Minerva arm (Test) of 81%, the required sample size was 129 subjects (86 Test and 43 Control). Based on a projected 16% loss-to-follow-up rate, a total of up to 153 subjects (102 Test and 51 Control) was enrolled.

The null hypothesis specified that the clinical success rate for the Test device be inferior to the Control device by more than the noninferiority margin of 20%. Rejecting the null hypothesis indicates that the clinical success rate for the Test device is not less effective than the Control by more than the noninferiority margin of 20%. The SAP specified that superiority of the Test over the Control device would be tested in the case that noninferiority is claimed. All primary effectiveness and safety results were summarized for the intent-to-treat population, defined as all subjects randomized and in whom treatment was attempted, whether successful or not.

The study of the Minerva System was conducted at 13 clinical sites. Pooling the data was justified by implementation of identical protocols, data-gathering methods, and study compliance monitoring across all clinical sites, with the methodology described by Meinert [29]. In addition, the FDA requires a test of homogeneity of odds ratios across investigational sites. The test for homogeneity was based on a 2-sided test at the .10 level of significance.

Demographic and baseline characteristics were summarized descriptively. Additional statistical analyses were conducted in strict compliance with the SAP. Data analysis was performed by independent biostatisticians (R.P. Chiacchierini Consulting, Gaithersburg, MD, and Willes Consulting Group, Inc., Encinitas, CA) using SAS version 9.2 or later (SAS Institute Inc., Cary, NC).

Menstrual Blood Loss Assessment

Menstrual blood loss was quantitatively measured for study inclusion and postoperatively at 6 and 12 months post-procedure. Various feminine sanitary product brands (Kotex Maxi Pads [Kimberly-Clark , Irving, TX], Tampax Flushable Tampons [Procter & Gamble, Cincinnati, OH], Carefree Original and Body Shape Pantiliners [Johnson & Johnson, New Brunswick, NJ]) were supplied to each study subject, and a validated AH analysis method [30,31] successfully applied in a large number of other similar studies [32–34] was used. Study subjects were required to collect used sanitary products and blood clots using a special sanitary product collection kit. The used sanitary products were delivered to and inventoried by the clinical site before being shipped to a central laboratory (KCAS Bioanalytical Services, LLC, Shawnee, KS), which performed the AH analysis of the menstrual sanitary products.

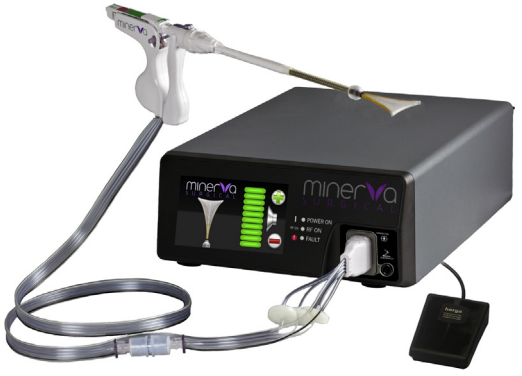
Inclusion and Exclusion Criteria

Subjects were required to be premenopausal (follicle-stimulating hormone level $\leq$ 40 mIU/mL), between 25 and 50 years of age, to have completed childbearing, and to provide AH documented evidence of HMB (PALM-COEIN: E, O). Bleeding levels were assessed preoperatively, and all candidates had to satisfy a minimum bleeding level of 160 mL per cycle (for 1 cycle) to qualify for study participation. Uterine sounding length was limited to a maximum of 10 cm. During the follow-up period, subjects were prohibited from using any form of hormonal birth control to eliminate the possibility of post-treatment bleeding reduction induced by the suppressive action of hormonal contraceptives.

Evidence of pelvic inflammatory disease, active/acute endometritis, sexually transmitted infections, bacteremia, sepsis, other active local and/or systemic infection, untreated/unevaluated cervical dysplasia (except CIN I), endometrial hyperplasia, or known or suspected abdominal or pelvic cancer were all exclusionary in this study. Subjects with suspected or known coagulopathies, on anticoagulation therapy, or diagnosed with congenital malformations of the uterus, hysteroscopically or ultrasonographically confirmed fibroid(s) distorting the uterine cavity, endometrial polyp(s) larger than 2 cm, or if less than 6 weeks post-partum were excluded from study participation. Subjects with a history of prior uterine surgery (except low segment cesarean delivery) that interrupts the integrity of the uterine wall (e.g., transmural myomectomy or classical cesarean section), as well as those with the history of previous endometrial ablation were excluded from study participation. Also excluded were subjects that had

Fig. 1

Minerva Endometrial Ablation System.



an implantable contraceptive device (e.g., Essure or Adiana) and those that were on medications that could thin the myometrial muscle, such as long-term steroid use (except inhaler or nasal therapy for asthma).

Minerva Endometrial Ablation System and Rollerball Ablation

The Minerva Endometrial Ablation System (Fig. 1) is designed to treat HMB in premenopausal women for whom childbearing is complete. It consists of the Minerva Surgical Radio Frequency Controller and the Endometrial Ablation Disposable Handpiece. The system uses Argon plasma technology to ablate tissue using 3 simultaneous and complimentary ablation methods: tissue-penetrating bipolar radiofrequency energy, direct-contact thermal ablation from membrane to tissue, and thermal ablation using the heated remnant liquids (blood, saline, other) present in the uterine cavity. Detailed description of the Minerva Endometrial Ablation System is available elsewhere [24].

Rollerball ablation is a resectoscopic ablation technique first described by Vancaille in 1989 [35]. Since then it has been extensively evaluated in a large number of RCTs and other studies demonstrating very good immediate and long-term clinical results. As a result, rollerball ablation established itself and has remained the gold standard, and it is the procedure that served as a control for all subsequently developed nonresectoscopic endometrial ablation technologies [4–13,36].

Patients

In total, 153 subjects were enrolled at 13 clinical sites. Subjects were randomized to the Test or Control Groups at the time of study enrollment, and all subjects were treated as per the randomization assignment. All 153 subjects were treated: 102 subjects in the Minerva Endometrial Ablation System Test Group and 51 subjects in the rollerball ablation Control Group. Table 1 lists the baseline demographics

Table 1

Baseline demographics and gynecologic history

Subject characteristic	Minerva (n = 102)	Rollerball (n = 51)	p
Age, yr			
Mean ± SD (median)	42.6 ± 4.2 (42.9)	42.5 ± 4.7 (43.1)	.97
Range (min–max)	31.6–50.1	32.3–49.3	
Race			
American Indian or Alaskan Native	1 (1.0%)	0 (.0%)	1.00
Black or African American	3 (2.9%)	2 (3.9%)	
White	98 (96.1%)	49 (96.1%)	
Ethnicity			
Hispanic or Latino	30 (29.4%)	15 (29.4%)	1.00
Not Hispanic or Latino	72 (70.6%)	36 (70.6%)	
Body mass index, kg/m^2			
Mean ± SD (median)	30.0 ± 7.1 (29.7)	28.8 ± 5.3 (28.6)	.28
Range (min–max)	16.6–52.1	19.8–40.6	
Reproductive history			
Gravida			
Mean ± SD (median)	3.1 ± 1.7 (3)	3.3 ± 1.5 (3)	.65
Range (min–max)	.0–10.0	.0–7.0	
Para			
Mean ± SD (median)	2.6 ± 1.3 (3)	2.5 ± 1.2 (2)	.65
Range (min–max)	.0– 9.0	.0–6.0	
Menstrual history			
Regular cycle pattern	97 (95.1%)	48 (94.1%)	1.00
Dysmenorrhea	57 (55.9%)	32 (62.7%)	.49
PMS	66 (64.7%)	35 (68.6%)	.72
AH value at baseline			
Mean ± SD (median)	310.2 ± 169.0 (247.5)	301.8 ± 176.1 (249.0)	.78
Range (min–max)	161.5–1120.0	160.0–1026.1	
Laboratory results, FSH, IU/L			
Mean ± SD (median)	7.5 ± 5.5 (6.0)	8.0 ± 6.3 (6.0)	.60
Range (min–max)	1.0–30.0	2.0–35.3	

SD = standard deviation; FSH = follicle-stimulating hormone.

Table 2

Operative procedure data

Parameter	Minerva (n = 102)	Rollerball (n = 51)	p
Sounding length, cm			
Mean ± SD (median)	8.9 ± .7 (9.0)	8.8 ± .7 (9.0)	.55
Range (min–max)	6.0–10.0	7.0–10.0	
Cavity length, cm			
Mean ± SD (median)	5.4 ± .6 (5.5)	5.4 ± .6 (5.5)	.90
Range (min–max)	4.0–6.5	4.0–6.5	
Cervical dilation, mm			
Mean ± SD (median)	6.8 ± 1.1 (7.0)	9.3 ± 1.5 (10.0)	<.0001
Range (min–max)	.0–9.0	.0–10.0	
Uterine position			
Anteverted	68 (66.7%)	35 (68.6%)	.52
Mid-position	15 (14.7%)	10 (19.6%)	
Retroverted	19 (18.6%)	6 (11.8%)	

SD = standard deviation.

and gynecologic history for the 153 enrolled subjects. All parameters were comparable between the treatment groups.

The homogeneity of the treatment effect across investigational sites at 12 months of follow-up was tested and was not rejected (p = .51). Because (1) the hypothesis of homogeneity of treatment effect across sites was justified, (2) subjects were randomized at each site, and (3) each investigational site conducted the study under a common protocol, data could be pooled across study sites to estimate a common treatment effect.

Table 3

Anesthesia regimen

Anesthesia type	Randomization arm: Minerva (n = 102)	Randomization arm: Rollerball (n = 51)
General	19 (18.6) [11.6, 27.6]	10 (19.6) [9.8, 33.1]
General/cervical block	0 (.0) [.0, 3.6]	1 (2.0) [.0, 10.4]
Intravenous	9 (8.8) [4.1, 16.1]	5 (9.8) [3.3, 21.4]
Intravenous/cervical block	49 (48.0) [38.0, 58.2]	27 (52.9) [38.5, 67.1]
Intravenous/cervical block/oral	7 (6.9) [2.8, 13.6]	3 (5.9) [1.2, 16.2]
Spinal block	7 (6.9) [2.8, 13.6]	0 (.0) [.0, 7.0]
Spinal block/ intravenous	11 (10.8) [5.5, 18.5]	5 (9.8) [3.3, 21.4]

Values are number of case with percents in parentheses and 95% confidence intervals in brackets.

Table 4

Rates of success and amenorrhea

Endpoint	Randomization arm: Minerva (n = 102)	Randomization arm: Rollerball (n = 51)
Success		
n (%)	95 (93.1)	41 (80.4)
95% CI	86.4, 97.2	66.9, 90.2
Upper 97.5% CI of the difference	–.80	
p	.02 (Fisher's exact test)	
Amenorrhea		
n (%)	73 (71.6)	25 (49.0)
95% CI	61.8, 80.1	34.8, 63.4
p	.01 (Fisher's exact test)	

CI = confidence interval.

Clinical Results

Procedure Data

The uterine sound and cavity lengths were comparable between the 2 treatment groups, as were the various uterine positions. Cervical dilation in the rollerball Control Group was statistically significantly greater than that reported for the Minerva Test Group (*t* test, p < .0001). Table 2 lists data collected during the procedure for the 153 enrolled subjects.

Study investigators were allowed to use the anesthesia regimens commonly employed in their practice as the standard of care. Table 3 demonstrates that the anesthesia regimens used were comparable between the treatment groups. The mean procedure time, defined as the time from device insertion to the time of device removal, for Minerva was 3.1 minutes, which was significantly less than the mean

Table 5

Rates of success and amenorrhea as a function of age

Arm	Age (yr)	Success: n	Success: %	Success: p	Amenorrhea: n	Amenorrhea: %	Amenorrhea: p
Minerva	≤40	34	94.4	.70	26	72.2	.91
	41+	61	92.4		47	71.2	
Rollerball	≤40	13	72.2	.70	8	44.4	.75
	41+	28	84.8		17	51.5	

procedure time in the rollerball group of 17.2 minutes (unequal variance *t* test, $p < .0001$).

Efficacy Results

The success rate at 1 year was 93.1% (95/102) for the Minerva Test Group compared with 80.4% for rollerball, with a difference of –12.7% and upper 1-sided 97.5% confidence limit of –.80%. Thus, the noninferiority null hypothesis was rejected because –.08% is lower than 20%. The test for superiority of Minerva over rollerball was done and concluded that the success rate in the Minerva Test Group was statistically significantly greater than in the rollerball Group (Fisher's exact test, $p = .02$).

The amenorrhea rate at 1 year was 71.6% (73/102) for the Minerva-treated subjects and 49% (25/51) for those treated with rollerball, with this difference also achieving statistical significance (Fisher's exact test, $p = .01$) (Table 4). Treatment failures included subjects with AH values > 80 mL, subjects who had any additional (medical and/or surgical) treatments or interventions for management of HMB during the follow-up period, and any subjects lost to follow-up.

The effect of age on success and amenorrhea for both treatment groups was also analyzed. At 1 year post-treatment, the success rates in the Minerva Test Group were 94.4% and 92.4% in the ≤40 and >40 age groups, respectively. At the same 1-year time point, the rollerball Control subjects reported success rates of 72.2% and 84.8%, respectively. The amenorrhea rates in the ≤40 and >40 age groups were 72.2% and 71.2% for Minerva Test Group and 44.4% and 51.5% for rollerball Control Group, respectively (Table 5). A logistic regression model for treatment success and amenorrhea rates was done and demonstrated that age did not significantly affect success rates or amenorrhea rates either by itself or in interaction with treatment.

During the first year of follow-up, 2 hysterectomies (1.96%) were performed in the Minerva Group, whereas 3 hysterectomies (5.9%) were required in the rollerball arm of the study. All hysterectomies (except 1 in the Minerva arm) were performed for continuing bleeding. One Minerva subject underwent hysterectomy because of pelvic inflammatory disease. A greater number of women in the rollerball arm required additional medical (oral contraceptives, tranexamic acid, Depo-Provera) and/or surgical treatment to control bleeding at 1 year than in the Minerva arm. All subjects who underwent hysterectomy were considered study failures during analysis. The rate of (medical + surgical) reintervention for HMB was 2.9% (95% confidence interval, .6%–8.4%) in the Minerva group, compared with 11.8% (95% confidence interval, 4.4%–23.9%) in the rollerball group; however, this difference was not statistically significant (Fisher's exact test, $p = .06$).

At 12 months postprocedure, 53.5% of Minerva subjects and 43.2% of rollerball subjects reported reduction in PMS. Dysmenorrhea reduction was reported by 46.5% of Minerva subjects and 45.5% of those treated with rollerball.

Safety Results

The safety of both procedures was evaluated by recording all AE. The numbers and percent of patients with serious AEs by time of occurrence are presented in Table 6 and nonserious AEs reported through the 12-month visit by device or procedural relationship are shown in Table 7. Investigators determined the relationship of the AE to the device and/or procedure. An AE that was "possibly," "probably," or "highly probably' related to the device or to the procedure was considered "related." Because no patient had more than 1 occurrence, Table 7 also represents the number of related AE occurrences. There have been no unanticipated device-related AEs in this study. All study participants adequately complied with the protocol requirement for contraception as evidenced by lack of unintended pregnancies during the follow-up period.

Patient Satisfaction

All subjects were asked about their level of satisfaction with their endometrial ablation treatment. A significantly higher rate of satisfaction was observed in the Minerva group at 91.9% versus 79.5% reported by the rollerball

Table 6

Number and percent of patients with serious AEs by time of occurrence

	Minerva (n = 102)			Rollerball (n = 51)		
AE	0–14 Days of procedure	15–30 Days of procedure	>30 Days of procedure	0–14 Days of procedure	15–30 Days of procedure	>30 Days of procedure
Bleeding	0 (.0%)	0 (.0%)	0 (.0%)	1 (2.0%)	0 (.0%)	0 (.0%)
Endometritis	0 (.0%)	0 (.0%)	0 (.0%)	1 (2.0%)	0 (.0%)	0 (.0%)
Pelvic inflammatory disease	0 (.0%)	0 (.0%)	1 (1.0%)	0 (.0%)	0 (.0%)	0 (.0%)
Other	1 (1.0%)	0 (.0%)	3 (2.9%)	0 (.0%)	1 (2.0%)	0 (.0%)

Table 7

Number and percent of patients with one or more related* AE by time of occurrence at 1 year

AE type	Minerva (n = 102)	Rollerball (n = 51)
Intraoperative AEs		
Skin rash and/or itching or burning sensation	1 (1.0%)	0 (.0%)
Postoperative AEs (<24 h)		
Bleeding or spotting	0 (.0%)	1 (2.0%)
Nausea and/or vomiting	0 (.0%)	1 (2.0%)
Weakness, fatigue, sleepiness, lack of concentration, dizziness	1 (1.0%)	0 (.0%)
Backache	1 (1.0%)	0 (.0%)
Fever	1 (1.0%)	0 (.0%)
Postoperative AEs (≥24 h to 2 wk)		
Abdominal pain and/or bloating	3 (2.9%)	1 (2.0%)
Pelvic pain	1 (1.0%)	0 (.0%)
Vaginal discharge and/or unpleasant vaginal smell or other abnormal sensation	1 (1.0%)	0 (.0%)
Weakness, fatigue, sleepiness, lack of concentration, dizziness	1 (1.0%)	1 (2.0%)
Constipation	0 (.0%)	1 (2.0%)
Endometritis or endomyometritis	1 (1.0%)	2 (3.9%)
Skin rash and/or itching or burning sensation	1 (1.0%)	1 (2.0%)
Postoperative AEs (>2 wk to 1 yr)		
Abdominal pain and/or bloating	0 (.0%)	1 (2.0%)
Pelvic inflammatory disease	1 (1.0%)	0 (.0%)
Hematometra	1 (1.0%)	0 (.0%)
Dysmenorrhea	0 (.0%)	1 (2.0%)

* Possibly, probably, or highly probably related to device or procedure.

patients at 1 year postprocedure (Fisher's exact test, $p < .05$). The subjects were also asked if they would recommend the procedure to a friend or relative. At 1 year after the treatment, 94.9% of the Minerva patients and 88.6% of the rollerball ablation patients reported they would recommend the procedure to a friend or relative with a similar problem (Fisher's exact test, $p = .28$).

Other Results

Use of the Minerva device was rated as "excellent" in 98% of cases, "good" in 1%, and "fair" in the remaining 1%. Investigators found the Minerva device to be easy to insert and deploy and requiring minimal to no seating manipulation. Utilization of the cervical sealing balloon for the purpose of cervical canal occlusion during the Uterine Integrity Test [24] was found to be adequate.

Discussion

As with any RCT design, this study has a number of strengths. The prospective study conduct allows for specific allocation and administration of interventions to a chosen population, thus reducing any allocation bias. Randomization reduces selection bias and enables the variance of the groups to be matched while reducing confounders. In addition, multicenter trials tend to have a greater clinical applicability and effectively address the drawbacks of single-center design studies, results of which are rarely confirmed and/or replicated in an RCT environment. Use of the intent-to treat approach in calculation of the primary and secondary endpoints with statistical methods clearly defined by the SAP ensured that the reported outcome data are conservative in nature. Subject retention in the study was good, with 6.5% of subjects exiting the study before the 1-year follow-up. This compares favorably with the reported loss to follow-up rates of up to 18% in similar clinical trials [7,37,38].

The use of AH as a validated, quantitative, highly precise, and accurate method for assessment of blood loss is a major strength of this research. Methodologically, AH compares favorably with the time-tested, but qualitative, binary in nature (HMB vs non-HMB), and less accurate Pictorial Blood Loss Assessment Chart method [39].

A weakness of this study is that, like other similar studies, this research effort does not represent core research on the subject of the underlying medical condition but is rather limited to assessment of safety and efficacy of 2 devices designed to treat it. As such, the design of this and similar studies cannot and should not be viewed as an attempt to better understand the etiology and pathophysiology of HMB. Another potential weakness of this study is related to a disproportionally small enrollment of an African American population when compared with its prevalence within US population. Although there is no evidence that effectiveness of endometrial ablation is race sensitive, having positive proof of this in a study would be beneficial. Some may

also suggest that comparing any new device with rollerball, a procedure rarely performed these days, has declining merit and that a study comparing the Minerva amenorrhea and success rates of 71.6% and 93.1%, respectively, to the FDA-reported amenorrhea and success rates of today's commonly used endometrial ablation devices (NovaSure, 36% and 77.7% [12]; Genesys HTA, 35% and 68.4% [11]; and Her Option, 22.2% and 67.4% [10]) would be of greater value. We agree that such an RCT would be of interest and should be considered in the future.

Considering that patients suffering from coagulopathies and those on anticoagulation therapy were excluded in this study, a study assessing the performance of the Minerva system in this subset of patient population is of interest and should be considered as a subject of future research. The relatively short duration of follow-up of only 12 months can be viewed as a study weakness, because over a longer period of time there may be an increase in the rate of treatment failure, reintervention, and/or onset of dysmenorrhea, effects reported with other endometrial ablation technologies [40]. Therefore, a longer-term follow-up for this study is planned and once available will be reported.

The Minerva success rate of 93.1% is similar to the previously published Minerva Single Arm Study [24] success rate of 96.2%, effectively validating and confirming the results of this previous research effort in a more rigorous RCT environment. However, it is imperative to appreciate that to duplicate the reported results, strict compliance with all elements of patient selection criteria used in this study is paramount. It should also be noted that Minerva success rates were consistent and independent of the methodologies (Pictorial Blood Loss Assessment Chart vs AH) used for the assessment of the primary endpoints of the studies and/or overall study designs. The Minerva success rate of 93.1% is statistically superior to the success rate of 80.4% reported in the rollerball arm of the study. This statistical superiority is believed to be the first such observation where a nonresectoscopic endometrial ablation device was able to outperform the gold standard rollerball efficacy in an RCT setting. Therefore, we believe a confirmatory RCT validating these results would be of interest and benefit.

The Minerva reported amenorrhea rate of 71.6% was also statistically superior when compared with that of rollerball at 49% and is also in line with amenorrhea rate of 69.5% reported in previous research [24]. Other research in the field of endometrial ablation clearly suggests that amenorrhea strongly correlates with high patient satisfaction [41], whereas lack of amenorrhea commonly leads to hysterectomy [42]. The rate of hysterectomy in the Minerva arm of this study was lower than the rate in the rollerball arm. Pathology reports indicated that in four of five subjects who underwent hysterectomy, adenomyosis was present in the extirpated specimen. Although this information is in line with other clinical reports on this subject, we believe that drawing unequivocal conclusions about the role of adenomyosis in the rate of failure and subsequent hysterectomy after endometrial ablation is premature, because it is unclear how many subjects with adenomyosis were successes in this study and avoided hysterectomy. Patient satisfaction, currently considered by many as the key performance data point and the most important clinical validator of success, was statistically significantly higher in the Minerva-treated subjects than in the rollerball-treated subjects.

Reduction in PMS and dysmenorrhea was observed in both arms of the study with no significant difference in the degree of such reductions. Similarly to other studies that reported on PMS and dysmenorrhea, the data derived on the reported reduction did not use a validated questionnaire and are qualitative in nature. Although fully expected and reported in previous endometrial ablation related research with these and other devices, the exact mechanism responsible for these reductions remains unknown. Some investigators in this study theorized and elaborated on the possible mechanisms behind these observations and presented them elsewhere [24].

Procedure time for both procedures was short. On average, the total time from device insertion to device removal for Minerva was 3.1 minutes, which was significantly less than the very respectable 17.2 minutes for rollerball. The degree of cervical dilation required to accommodate the Minerva device was statistically less than for rollerball, which has the potential of reducing the incidence of unintended iatrogenic injuries (e.g., laceration) to the cervix and/or the endocervical canal.

In conclusion, the results of this multicenter RCT demonstrate that at 12-month follow-up the Minerva procedure produces statistically significantly higher rates of success, amenorrhea, and patient satisfaction as well as a shorter procedure time compared with the criterion standard rollerball ablation. Safety results were excellent and similar for both procedures. Results of this study replicate the results of previously published research, effectively confirming that the Minerva procedure should be considered as a minimally invasive treatment method when managing HMB unrelated to anatomic causes.

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