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Novasure impedance control system versus microwave endometrial ablation for the treatment of dysfunctional uterine bleeding: a double-blind, randomized controlled trial

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Summary

Purpose of investigation: To compare the efficacy and safety of two different second-generation ablation devices, Novasure impedance control system and microwave endometrial ablation (MEA), in cases of abnormal uterine bleeding (AUB). *Materials and Methods:* This is a randomized controlled trial that took place in a single Gynecological Department of a University Hospital. Sixty-six women with dysfunctional uterine bleeding (DUB), unresponsive to medical treatment, were included in the trial. The ratio of women allocated to bipolar radio-frequency ablation or MEA was 1:1. Follow-up assessments were carried out at three and 12 months post-ablation. The present main outcome measure was amenorrhea rates 12-months post-treatment. *Results:* The rate of amenorrhea at 12-months post-ablation was significantly higher in women treated by Novasure (25/33; 75.8%) as compared to those treated by MEA (8/33; 24.2%) (rate difference: +51.5%, 95% CI: +27.8 to +67.7). *Conclusion:* In women with DUB, endometrial ablation with Novasure bipolar radiofrequency impedance-controlled system is associated with increased rates of amenorrhea at 12-months post-treatment as compared to the MEA method.

Key words: Abnormal uterine bleeding; Novasure; Microwave endometrial ablation.

Introduction

Abnormal uterine bleeding (AUB) is one of the most common problems in women of reproductive age, with a prevalence of more than 5% [1]. It is estimated that menorrhagia affects 10-30% of menstruating women at any time [2] and about 20% of referrals of women to their gynecologists are due to menstrual disorders [3].

AUB may be due to anatomical, endocrine, hematological and iatrogenic factors, although several cases of AUB occur without any obvious pathology. The latter was usually referred under the name of dysfunctional uterine bleeding (DUB), which accounts for about half the cases of excessive menstrual blood loss [4]. Since 2011 with the FIGO classification system (PALM-COEIN terminology) [5] in cases of AUB the term DUB was discouraged, although it is still commonly used throughout the gynecological community. Nowadays nonstructural causes of AUB, as well as non-identified disorders of hemostasis (AUB-C), ovulatory disorders (AUB-O), endometrial disorders (AUB-E), and non-classified causes (AUB-N) compose the large group of what we used to categorize as DUB.

Several treatment options have been proposed in cases of AUB. Medical treatment is considered as a first-line treatment and includes tranexamic acid, non-steroidal anti-inflammatory drugs, combined oral contraception pill, progestogen, danazol, gonadotropin releasing hormone analogues (GnRH-a), and levonorgestrel releasing intra-uterine system. In cases of AUB resistant to medical treatment, physicians should offer women an alternative surgical treatment, choosing between hysteroscopic and non-hysteroscopic endometrial ablation techniques and hysterectomy [6].

The effectiveness of the reported treatment options for AUB has been evaluated and reviewed in many publications. Surprisingly there is lack of randomized controlled trials (RCTs) comparing most of the ablation devices. Due to this fact, recently, a systematic review had to employ methods of network meta-analysis in order to provide indirect evidence regarding the comparative efficacy of many second-generation ablation devices [7].

The aim of this randomized controlled trial is to compare the efficacy and safety of two different second-generation ablation devices, Novasure impedance control system and microwave endometrial ablation (MEA), in cases of DUB.

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Materials and Methods

A randomized controlled trial was performed in the 1st Department of Obstetrics and Gynecology, "Papageorgiou" University Hospital of Thessaloniki, Greece from January 2008 until December 2010. Both ethics committees of the hospital and the Aristotle University of Thessaloniki approved the study, while at the same time the protocol of this RCT was registered in ClinicalTrials.gov (ID: NCT01173965).

Population

Women with DUB, as indicated on the pictorial blood assessment chart (PBAC) described by Higham *et al.* [8] with a score of more than 150 points, were eligible for the trial. All women included in the trial suffered from AUB for more than a year, unresponsive to medical therapy, and had already completed their family planning. All patients were younger than 50 years old, had to have a normal cervical cytology test, a negative pregnancy test, and a follicular stimulating hormone (FSH) level of less than 20 mIU/ml. Women with coagulopathies or thyroid gland dysfunction were excluded from the trial. In order to exclude uterine pathology, all women were subjected to transvaginal ultrasound scan and endometrial biopsy (either by dilatation and curettage or hysteroscopy).

Interventions and outcomes

After signed informed consent was obtained, every patient was scheduled for surgical intervention. Demographic data of each patient were registered, as well as data regarding the history and the clinical condition of their AUB. The presence of dysmenorrhea was also recorded and its intensity was determined by means of a visual analogue scale (VAS). Pre-treatment of the endometrium with three monthly doses of 3.75 mg leuprolide acetate was performed in all patients before randomization, which was undertaken with the use of a computer-generated table of random numbers. Although usage of GnRH-a is not recommended in cases of Novasure ablation, according to guidelines, in order to insure patient blinding to the allocated treatment, the authors prescribed GnRH-a to all patients. To ensure allocation concealment, this table of random numbers was not disclosed to the recruiting physicians. The ratio of women allocated to bipolar radio-frequency ablation or microwave endometrial ablation was 1:1.

The ablation treatment in both groups was performed by an experienced senior gynecologist according to the instructions of the manufacturers. The procedures were carried out as day-cases, under general intravenous anesthesia. Analgesia was pursued with the administration of 40 mg parecoxib sodium intramuscularly during treatment. The duration of each treatment was recorded by each device as net ablation time. The patients were blind to the allocated ablation technique.

Follow-up assessments were carried out at three and 12 months post-ablation. At three months after the procedure, women were contacted by telephone and interviewed. They were asked to report whether: a) they were amenorrhoic or not, b) there was need for analgesics immediate post-ablation, c) they were experiencing dysmenorrhea or not, d) they would consider that their clinical condition improved or not and, e) whether they were satisfied with the method or not. At 12-months post-ablation, patients were asked to visit the out-patient clinic of the University department. During this visit, a physician who was unaware of the allocated treatment modality examined the women. Duration and clinical characteristics of menstruation were registered, as well as information concerning patient satisfaction and potential improvement (or not) in everyday life. At the same time, a Higham's pictorial chart was also completed [8]. The presence of amenorrhea at 12-months post-ablation was the primary outcome measure. Furthermore, it was noted whether another additional intervention or hysterectomy had been performed during this time due to method failure.

Power analysis

Since at the time of protocol set-up there was no published data on the efficacy of MEA, explicitly on women with DUB, an analysis of ten such cases treated with MEA in the present department, provided the best estimate for the proportion of patients with amenorrhea at 12 months post-ablation (20%). Regarding the efficacy of Novasure, data from a published RCT were used [9]. Based on these assumptions, it was estimated that 33 patients in each group would be sufficient to detect a difference in the efficacy of the two methods (achievement of amenorrhea at 12-months after treatment) from 0.20 (MEA) to 0.56 (Novasure) [9] using a two-tailed Fisher's Exact test with a=0.05 and b=0.20.

Statistical analysis

The normality of distribution of continuous variables was tested with the use of the Shapiro-Wilk test. In case of normal distribution of values, the results between the two groups were compared with the use of Student's t-test, whereas in case of non-normality, the Mann-Whitney U test was used. Categorical variables were compared between groups with the use of the Fisher's Exact test. All analyses were performed according to the intention-to-treat principle. Statistical significance was set at a level of 0.05. The Statistical Program for Social Sciences was used for all statistical analyses.

Results

According to the recruitment plan, 66 patients were enrolled in this study (MEA: n=33 – Novasure: n=33). Every patient was treated according to the group that was allocated to by the randomization table. The minimum follow-up of 12 months after treatment was completed by all randomized patients.

The baseline characteristics of the population analyzed in this study are depicted in Table 1. Overall, no statistically significant differences were observed between the two groups compared in terms of age, weight and body mass index (BMI), as well as, in number of previous pregnancies, menstruation patterns, and previous history of AUB. Similarly, the mean concentration of hemoglobin (as assessed during the initial work-up) was comparable between the two arms of this study.

Regarding treatment characteristics (Table 2), the length of the procedure was significantly increased in the MEA group. Endometrial ablation using either Novasure or MEA was successfully performed in all cases, while no major or minor complications were noted in the patients included in this RCT. The use of analgesics immediate post-ablation was required more often in patients treated with MEA as compared to those in whom Novasure was used (Table 2).

Follow-up at three months

All 66 patients had a follow-up telephone interview at three months after the endometrial ablation procedure (Table 3). Less women reported dysmenorrhea in the No-

Table 1. — *Baseline characteristics.*

	MEA (n=33)	Novasure (n=33)	*p*
Age (years)[a]	46.0 (5)	45.0 (5)	0.99
Weight (kg)[b]	71.6 (8.0)	69.2 (12.7)	0.36
BMI (kg/m^2)[b]	27.3 (3.0)	26.1 (4.6)	0.22
Gravida[c]	*1:* 10 *2:* 19 *3:* 4 *4:* 0	*1:* 10 *2:* 21 *3:* 1 *4:* 1	0.50
Menstruation (days)[a]	7 (1)	7 (2)	0.56
PBAC[b]	554 (119.1)	622 (218.6)	0.12
Dysmenorrhea[c]	Yes: 17 No: 16	Yes: 17 No: 16	1.0
VAS[a]	4 (7)	3 (5)	0.61
Hgb (g/dL)[a]	11.3 (0.7)	11.2 (2.2)	0.81

[a]: Results are presented as median (interquartile range) and compared with Mann Whitney U test; [b]: Results are presented as mean (standard deviation) and compared with the Student' s t-test; [c]: Results are presented as counts and compared with the Fisher's Exact test.

Table 2. — *Treatment parameters.*

	MEA (n=33)	Novasure (n=33)	*p*
Duration of treatment[a] (sec)	76.8 (9)	67.0 (19)	<0.001
Minor complications[b]	Yes: 33 No: 0	Yes: 33 No: 0	n/a
Major complications[b]	Yes: 33 No: 0	Yes: 33 No: 0	n/a
Use of analgesics post-ablation[c]	Yes: 9 No: 24	Yes: 0 No: 33	0.002

[a]: Results are presented as median (interquartile range) and compared with Mann Whitney U test; [b]: Results are presented as counts; [c]: Results are presented as counts and compared with the Fisher's Exact test. n/a: not applicable.

Table 3. — *Follow-up at three months.*

	MEA (n=33)	Novasure (n=33)	*p*
Dysmenorrhea[a]	Yes: 4 No: 31	Yes: 2 No: 29	0.67
Subjective blood loss[a]	Amenorrhea: 9	Amenorrhea: 22	0.003
Clinical status improvement[a]	Yes: 32 No: 1	Yes: 33 No: 0	1.0
Method satisfaction[a]	Yes: 32 No: 1	Yes: 33 No: 0	1.0

[a]: Results are presented as counts and compared with the Fisher's Exact test.

Table 4. — *Follow-up at 12 months.*

	MEA (n=33)	Novasure (n=33)	*p*
Dysmenorrhea[a]	Yes: 8 No: 25	Yes: 2 No: 31	0.08
VAS[b]	1.0 (4)	0 (1)	0.75
Subjective blood loss[a]	Amenorrhea: 8 Hypomenorrhea: 16 Cryptomenorrhea: 1 Eumenorrhea: 3 Menorrhagia: 5	Amenorrhea: 25 Hypomenorrhea: 3 Cryptomenorrhea: 0 Eumenorrhea: 4 Menorrhagia: 1	<0.001
PBAC[b]	12.0 (77)	0 (4)	<0.001
Difference in PBAC score[b]	- 465.0 (182)	- 595.0 (218)	0.016
Hgb (g/dL)[c]	12.9 (0.99)	12.9 (1.03)	0.90
Method satisfaction[a]	Yes: 28 No: 5	Yes: 33 No: 0	0.053
Improvement in everyday life[a]	Yes: 30 No: 3	Yes: 33 No: 0	0.24
Need for further treatment[a]	Yes: 2 No: 31	Yes: 0 No: 33	0.49

[a]: Results are presented as counts and compared with the Fisher's Exact test; [b]: Results are presented as median (interquartile range) and compared with Mann Whitney U test; [c]: Results are presented as mean (standard deviation) and compared with the Student' s t-test.

vasure group (n=2) as compared to the MEA group (n=4), although this difference was not statistically significant (rate difference: -6.1%, 95% CI: -21.9 to +9.3). Most of patients in the Novasure group (n=22) reported amenorrhea, while only few patients in the MEA group (n=9) respectively (p = 0.003) (Table 3). In terms of clinical improvement and patient satisfaction both methods had similar rates (MEA: 97% *vs.* Novasure: 100%).

Follow-up at 12 months

Twelve months after the endometrial ablation, all patients (n=66) returned for a follow-up visit. Dysmenorrhea was reported more often from patients who were treated with MEA, yet this difference was not statistically significant (rate difference: +18.2%, 95% CI: -0.5 to +35.5) (Table 4). Similarly, the intensity of the pain, as measured by the VAS was not significantly different.

The rate of amenorrhea at 12-months post-ablation was significantly higher in women treated by Novasure (25/33; 75.8%) as compared to those treated by MEA (8/33; 24.2%) (rate difference: +51.5%, 95% CI: +27.8 to +67.7). Overall, the profile of blood loss seemed to be more favorable in women treated by Novasure (Table 4). In line with this finding, was the fact that the PBAC score was significantly decreased in the Novasure group when compared with the MEA group and that the mean difference in this score for each group from recruitment to 12-months post-ablation was significantly higher in the Novasure group. The mean level of hemoglobin was not significantly different in the two groups (Table 4).

Finally, more patients in the Novasure group (33/33; 100%) reported that they were satisfied with the results of the procedure, when compared with the MEA group (28/33; 84.8%), and this difference was marginally significant (p = 0.053). An improvement in everyday life was noted by a high proportion of patients in both groups (Novasure: 33/33 vs. MEA: 30/33; p = 0.24).

Two out of 33 patients in the MEA group required an additional treatment before their 12-month follow-up visit (Table 4). One presented cryptomenorrhea five months

post-ablation and was treated by hysterectomy, while the second woman presented continuous menorrhagia and requested permanent treatment by hysterectomy ten months after her primary treatment. No patient had been submitted to an additional intervention in the Novasure group. The only patient in this group that was still experiencing menorrhagia based on her PBAC score, reported a significant improvement as compared to her clinical status before entering the study (PBAC difference: -603.0) and was unwilling to undergo further treatment.

Discussion

This RCT comes to the conclusion that, in women with DUB, endometrial ablation with the Novasure bipolar radiofrequency impedance-controlled system is associated with increased rates of amenorrhea at 12-months post-treatment as compared to the MEA method.

The superiority of Novasure in terms of amenorrhea achievement was evident from the first follow-up interview, already at three-months post-treatment. Furthermore, it seems that most of the therapeutic potential of either Novasure or MEA is expressed as early as three-months post-treatment and this finding appears to be in line with the available evidence [9-11].

It should be noted though, that at three-months post-treatment, most of the patients in the MEA group that did not achieve amenorrhea, reported hypomenorrhea. This might be the reason that led most of the patients in both groups reporting a substantial improvement in their clinical condition and expressing their satisfaction with the method of endometrial ablation.

Both methods appeared to be equally safe, since no major or minor complications were noted in any of the two groups. The Novasure method was completed in less time than what was required for MEA. However, this difference in time is small, and it is not likely to be of clinical importance. The use of analgesics postoperatively was more frequent in the MEA group as compared to the Novasure group (RD: +27.3%, 95% CI: +11.2 to +44.2).

To the best of the authors' knowledge the present is the first RCT comparing these two second-generation techniques of endometrial ablation (i.e. Novasure *vs.* MEA). Most RCTs that have been published so far have compared second with first generation devices of endometrial ablation [12-18]. Only five RCTs evaluating second-generation devices are available in the literature [9-11, 19, 20]. These include head-to-head comparisons between: a) Novasure bipolar radiofrequency impedance-controlled endometrial ablation and thermal balloon [9, 10, 20] b) Novasure bipolar radiofrequency impedance-controlled endometrial ablation and hydrothermoablation [19] and, c) MEA and thermal balloon [11].

These studies have been reviewed and meta-analyzed in a recent publication [7]. Based on the results of this meta-analysis, Novasure bipolar radiofrequency impedance-controlled endometrial ablation was associated with increased amenorrhea rates at 12-months post-treatment as compared to thermal balloon (OR: 4.56, 95% CI: 2.24-9.26). At the same time, direct evidence did not indicate a significant difference between MEA and the thermal balloon (OR: 1.13, 95% CI: 0.70-1.82), although a network meta-analysis performed suggested that potentially the MEA is superior to the thermal balloon in terms of amenorrhea at 12-months post-ablation (OR: 1.66, 95% CI: 1.01-2.71).

Regarding the comparison of Novasure with MEA, indirect evidence produced through a network meta-analysis suggested that MEA might be associated with decreased rates of amenorrhea at 12-months as compared to Novasure, although this result was not statistically significant (OR: 0.66, 95% CI: 0.36-1.21) [7]. The data from the present study seem to confirm the direction of the effect that was previously suggested through that indirect evidence.

One of the strong points of this study is the fact that the population analyzed was exclusively women with DUB. Most of the studies that have been published so far have not specifically targeted this population and have, in general, included women with abnormal menstrual bleeding due to various pathologies. Furthermore, according to the pre-specified inclusion/exclusion criteria, all women that were included in this RCT should have had a basal FSH less than 20 IU/L. In this way, the possibility of peri-menopausal amenorrhea during the follow-up period was reduced and thus, the actual efficacy of the two methods was evaluated. On the other hand, the present study is also characterized by some limitations that need to be commented. Although, the sample size of this study had been decided a priori based on a proper power analysis, it is not large, and thus, relatively wide confidence intervals have been produced. Evidently, the accumulation of high quality evidence in the future will produce a much more accurate estimate of the underlying effect size.

Another issue that the present authors had to take under consideration was whether to pre-treat endometrium with GnRH-a to all patients, or just women in MEA group, since thinning of the endometrium prior to the application of Novasure is not recommended according to guidelines. They decided to prescribe GnRH-a to all patients in order to insure patient blinding to the allocated treatment. In the present authors' opinion, pretreatment might play a small but crucial role in the final results by improving amenorrhea rates in Novasure group, but more evidence is needed to prove their hypothesis.

Conclusion

This study is the first to provide evidence on the comparative efficacy of the Novasure bipolar radiofrequency impedance-controlled system and MEA. Based on the re-

sults of this RCT, Novasure seems to be associated with increased rates of amenorrhea at 12-months after the procedure as compared to the MEA.

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