Excessive menstrual bleeding is often incapacitating, costly to treat, and socially embarrassing. It most often occurs in women over 35 years of age and accounts for more than one-third of hysterectomies performed annually in the United States. Affecting more than 10 million American women, the prevalence of menorrhagia was estimated at 22% among otherwise healthy women.1–3

Numerous large-scale studies assessed the safety, efficacy, and cost of endometrial ablation as an alternative to hysterectomy in treatment of menorrhagia.4–7 Laser ablation and then rollerball ablation laid the ground for rapid development of second-generation global endometrial ablation. These technologies were evaluated in randomized controlled studies8–10 to assess their efficacy compared with rollerball ablation. Although various aspects of these systems’ performance and their impact on the clinical outcome have been addressed, no clinical studies to date specifically addressed intraoperative and postoperative pain associated with these second-generation procedures.

Materials and Methods

This was a prospective, multicenter, international clinical trial at four investigational sites (3 in Canada, 1 in Germany). All investigators were gynecologic surgeons with extensive experience in performing endometrial ablation and who received training in use of both NovaSure and ThermaChoice. Each site’s institutional review board or ethics committee approved the investigation, and all patients provided signed informed consent before undergoing screening procedures and treatment.

We assessed and compared intraoperative and postoperative pain associated with two second-generation ablation systems, NovaSure impedance-controlled endometrial ablation with NovaSure and ThermaChoice system, and endometrial ablation with NovaSure could become an office-based procedure.

Assessment and Comparison of Intraoperative and Postoperative Pain Associated with NovaSure and ThermaChoice Endometrial Ablation Systems

P. Y. Laberge, M.D., R. Sabbah, M.D., C. Fortin, M.D., and A. Gallinat, M.D.

Abstract

Study Objective. To assess and compare intraoperative and postoperative pain associated with NovaSure impedance-controlled endometrial ablation system and ThermaChoice system.

Design. Prospective, international, multicenter, double-arm study (Canadian Task Force classification II-1).

Setting. Academic medical centers and private offices.

Patients. Sixty-seven premenopausal women with menorrhagia. Endometrial ablation with either the NovaSure (37 women) or ThermaChoice (30) system. NovaSure-treated patients received no endometrial pretreatment; those treated with ThermaChoice received the recommended 3-minute suction dilation and curettage.

Measurements and Main Results. Standard pain measurement instruments (visual analog scale, numeric rating scale) were used to assess intraoperative and postoperative pain. Serum levels of prostaglandin-F2α were measured before and 5, 30, and 60 minutes after the procedure. Patients treated with the NovaSure system reported statistically significantly lower intraoperative and postoperative pain than those treated with the ThermaChoice system (p <0.0001). Procedure time was statistically significantly shorter with the NovaSure system (p <0.0001). Prostaglandin-F2α values did not differ statistically between groups.

Conclusion. The NovaSure system is associated with statistically significantly lower intraoperative and postoperative pain than ThermaChoice system, and endometrial ablation with NovaSure could become an office-based procedure.
system (Novacept, Palo Alto, CA) and ThermaChoice (Gynecare, Menlo Park, CA), in women experiencing excessive menstrual bleeding. Pain was rated by visual analog scale (VAS), numeric rating scale (NRS), and brief pain inventory form. The secondary end point of the study determined the effect on and correlation of prostaglandin (PG)F2α serum concentrations with intraoperative and postoperative pain. The vasococonstructive and muscle-constricting activities of prostaglandins contribute to normal sloughing of the endometrial lining during menstruation. However, excessive production of prostaglandins in the uterine endometrium is involved in the cycle of pain, cramping, vomiting, and diarrhea. Assuming that PGF2α generated during tissue destruction is responsible for pain associated with endometrial ablation, higher pain levels on VAS and NRS were expected to correlate with higher concentrations of PGF2α in patients’ circulation.

Subjects
The 67 subjects (age 25–50 yrs) received a diagnosis of menorrhagia. Screening consisted of pelvic examination and assessment of the uterine cavity, blood chemistry, assessment of the uterine cavity, blood chemistry, sex hormone concentrations with intraoperative and postoperative pain. The vasococonstructive and muscle-constricting activities of prostaglandins contribute to normal sloughing of the endometrial lining during menstruation. However, excessive production of prostaglandins in the uterine endometrium is involved in the cycle of pain, cramping, vomiting, and diarrhea. Assuming that PGF2α generated during tissue destruction is responsible for pain associated with endometrial ablation, higher pain levels on VAS and NRS were expected to correlate with higher concentrations of PGF2α in patients’ circulation.

Pain Assessment
The VAS consists of a 10-cm horizontal or vertical line with two end points labeled no pain and worst pain ever experienced. The patient is asked to place a mark on the line that corresponds to the current level of pain and the distance from “no pain” to the mark is measured. Major advantages of the VAS as a measure of pain intensity are its ratio scale properties and its ease of application. The major disadvantage is its assumption that pain is a one-dimensional experience. The NRS requires the patient to choose a number between zero and 10 to represent pain. Only the extreme ends of the scale have word descriptions (0 = no pain, 10 = worst possible pain). Both instruments are assumed to be interval scales.

Because this study appeared to be the first to measure pain associated with endometrial ablation and thus no historical data were available, no statistical model was used to calculate the number of patients required for the study to achieve an acceptable power level. Data on pain levels were collected before and during the procedure, and 5, 15, 30, 60, 90, 120, 150, and 180 minutes after ablation.

Anesthesia
All study sites employed the same anesthesia regimens for both treatment groups. One hour before the procedure patients received a nonsteroidal antinflammatory drug rectal suppository. Intraoperative anesthesia consisted of a combination of paracervical block and intravenous sedation. The paracervical block was uniform for all patients and was calculated with the formula:

Patient’s weight (kg)/10 = number of ml lidocaine 2%.

The amount of calculated lidocaine 2% was then diluted with NaCl 0.9% up to 20 ml and partially injected intracervically at 2, 4, 7, and 10 o’clock positions. Two more injections of the remaining volume were applied in the area of uterosacral ligaments. On completing the block, the clinician waited 5 to 8 minutes to allow for sufficient anesthesia before beginning ablation.

Intravenous sedation was standard for both treatment groups and across all clinical sites. It consisted of fentanyl citrate 50 to 150 µg with or without midazolam HCl up to 2 mg. Mean doses for NovaSure-treated patients was 76.47 ± 41.71 µg and 0.85 ± 0.92 mg, respectively, and for ThermaChoice-treated women 75.0 ± 40.1 µg and 0.86 ± 0.99 mg, respectively. Data on postoperative anesthesia and analgesia requirements were also collected.

Data Analyses
Procedure and treatment times and cervical dilation required for each treatment modality were analyzed and compared. Two-tailed Student’s t test and analysis of variance for repeated measures were used for statistical analysis of data.

Ablation Procedures
The NovaSure system consists of a disposable electrode array, portable radio frequency (RF) controller, connecting cord, desiccant, foot switch, and power cord (Figure 1). It consists of a single-patient use, bipolar electrode array mounted on an expandable frame. During use, the device is inserted transcervically into the uterine cavity, and the protective sheath is retracted so the bipolar electrode array can be deployed and conform to the uterine cavity. The
The electrode array is formed from a gold-plated, porous fabric through which steam and moisture are continuously suctioned from desiccated tissue. NovaSure works in conjunction with a dedicated RF controller to perform a customized, global endometrial ablation in an average of approximately 90 seconds without need for concomitant hysteroscopic visualization or endometrial pretreatment. The specific configuration of the electrode array and predetermined power (specific to uterine cavity size) delivered by the controller create a tapered depth of ablation characterized by deeper ablation in the main body of the uterus and more shallow ablation profile in regions of the cornua and lower uterine segment. The controller automatically calculates the power output required based on individual uterine cavity size (length and width). These measurements are keyed into the controller by the operator. Intraoperative uterine sounding allows assessment of the length of the cavity, and the intrauterine measuring device, an integral component, measures uterine cavity width (cornu-to-cornu distance). A vacuum pump contained in the controller creates and maintains vacuum in the uterine cavity throughout the procedure, ensuring constant apposition between the electrode array and endometrium while simultaneously allowing for continuous removal of ablation by-products.

During the process, the flow of RF energy vaporizes and/or coagulates endometrium regardless of its thickness. As ablation continues, underlying superficial myometrium is also desiccated and coagulated. As tissue destruction reaches optimal depth for a safe and effective ablation, increasing tissue impedance causes the controller to terminate power delivery, thereby providing a self-regulating process. Monitoring tissue impedance automatically controls the depth of endomyometrial ablation. A cavity integrity-assessment system is an automatic safety feature to assist the physician in detecting uterine wall perforation and thus prevent energy delivery. Utilizing hysteroilator-type technology, carbon dioxide is delivered into the uterine cavity at a safe flow rate and pressure. Only when an intrauterine pressure of 50 mm Hg is reached and maintained for 4 seconds, confirming good uterine wall integrity, will the controller allow ablation to proceed.

The ThermaChoice system consists of an electronic controller, a single-use balloon catheter, and an umbilical cable (Figure 2). Before performing ablation, the system is set up, catheter primed, pressure titrated, and uterus sounded. The balloon catheter is inserted into the uterine cavity and filled with sterile 5% dextrose in water. The heating element is activated and temperature increases to 87°C within about 4 minutes. An 8-minute therapy cycle at that temperature allows for ablation of endometrial tissue. The controller automatically monitors the length of the procedure and

FIGURE 1. NovaSure impedance-controlled endometrial ablation system.
temperature within the balloon, terminating the treatment cycle after 8 minutes, which is confirmed by an audible sound. On successful completion of the procedure and cooldown cycle, fluid is evacuated from the balloon, which is then withdrawn from the uterine cavity.

**PGF$_{2\alpha}$ Concentrations**

Blood samples from each participant were collected before the procedure and 5, 30, and 60 minutes after endometrial ablation. Concentrations of PGF$_{2\alpha}$ were measured in plasma and/or serum samples using a Correlate-EIA PGF$_{2\alpha}$ immunoassay kit (Assay Designs, Inc., Ann Arbor, MI). The kit uses a polyclonal antibody against PGF$_{2\alpha}$ and competitively binds to PGF$_{2\alpha}$ in the sample or an alkaline phosphatase molecule that covalently attaches to PGF$_{2\alpha}$. After simultaneous incubation at room temperature, excess reagents are washed away and substrate is added. After incubation, the enzyme reaction is stopped and the generated yellow color is read on a microplate reader at 405 nm. The intensity of bound yellow color is inversely proportional to concentrations of PGF$_{2\alpha}$ in standards or samples. Measured optical density is used to calculate concentrations of PGF$_{2\alpha}$. Concentrations are calculated by comparing the optical density of the samples with a standard curve generated using known amounts of PGF$_{2\alpha}$.

Clinical laboratory variability in assessment of the PGF$_{2\alpha}$ values was eliminated by having a single laboratory (Assay Designs) assess all blood samples.

**Results**

Of 67 women, 37 were assigned to NovaSure treatment and 30 to ThermaChoice treatment. The groups were similar for demographic and gynecologic history variables (Table 1). No significant differences among any variables were found for either group across the four study sites, which allowed for pooling of data from all centers.

Since pain associated with each treatment modality and the time of patient exposure to pain differed significantly, we developed the intraoperative pain index that allows for a comparison of pain levels by factoring in time values. The index is calculated based on pain level multiplied by the time of patient exposure to pain in seconds. Application of this formula to the data can be visualized as two rectangles (one for each group) that represent pain level times ($\times$) time. By comparing the areas of the two rectangles, one can calculate how much one treatment modality differs from the other from the standpoint of patient suffering. Figures 3 and 4 show the intraoperative pain index for both treatments using mean values from VAS and NRS assessments.

A two-tailed Student’s $t$ test found a statistically significant difference in mean VAS values for the index between NovaSure and ThermaChoice ($p = 6.69838E-08$). The mean intraoperative pain index using VAS was 290.1 for NovaSure group compared with 2120.6 for ThermaChoice group. For the NRS, two-tailed Student’s $t$ test also found a statistically significant difference in mean

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<th>TABLE 1. Patient Demographics</th>
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<td>NovaSure ($n = 37$)</td>
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<td>Mean ± SD Range</td>
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<td>Age (yrs)</td>
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<td>Body weight (kg)</td>
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The intraoperative pain index between systems \( (p = 1.22605 \times 10^{-07}) \). The mean NRS pain index for NovaSure was 331.2 compared with 2108.6 for ThermaChoice. For both VAS and NRS mean values, the \( t \) test assumed unequal variances and an \( \alpha \) level of 0.05.

A different statistical test was employed to compare postoperative pain. Analysis of variance for repeated measures found a significant effect of time \( (p < 0.0001) \) and a significant effect of treatment \( (p < 0.0001) \), but no time-by-treatment interaction. In other words, the two groups were
significantly different independent of time. In addition, a significant change in VAS and NRS scores over time, independent of treatment, occurred with both groups, changing over time. Lack of a significant interaction term indicates that the groups changed over time in the same relative manner. Figures 5 and 6 show median values for postoperative pain levels for both groups using VAS and NRS assessments, revealing statistically lower pain associated with the NovaSure system (p < 0.0001).

NovaSure treatment also required significantly less time to perform (time from device insertion to device removal), with mean time of 2.5 ± 1.1 minutes, which was statistically significantly less than the 11.9 ± 2.1 minutes required for ThermaChoice ablation (p < 0.0001, Student’s t test). Treatment time, defined as the time during which energy was applied, averaged 1.5 ± 0.2 minutes for NovaSure ablation, compared with a preset 8 minutes for every ThermaChoice ablation. Mean cervical dilation for NovaSure-treated patients was 7.78 ± 0.25 mm and for ThermaChoice-treated patients was 6.31 ± 1.04 mm (p < 0.0001, Student’s t test).

No differences were found between groups with respect to PGE$_{2\alpha}$ levels. Postoperative values were stable over time (5, 30, and 60 min) compared with preoperative baseline values (Figure 7).

No serious intraoperative adverse events occurred in either group. However, significantly fewer patients treated with NovaSure (2, 5.4%) experienced postoperative nausea and vomiting compared with ThermaChoice-treated women (10, 33%, p < 0.0001, Student’s t test).

Ablations were completed in all 67 patients. Whereas 37 devices were used for 37 patients in the NovaSure group, 37 ThermaChoice devices were required to complete 30 procedures. Seven ThermaChoice devices could not be used due to breaches in the integrity of the balloon catheter, which did not allow for proper pressurization of the system.

**Discussion**

The goal of endometrial ablation is to provide less invasive, more effective, and less expensive treatment for menorrhagia and thus to avoid hysterectomy. Most new ablation systems do not require concomitant hysteroscopy. These technologies are faster and less complex and often allow for significant reduction in frequency of complications compared with the gold standard rollerball ablation. Some new technologies use heated liquid contained in a balloon inflated in the uterus$^{8,20}$ or injected directly into the uterine cavity.$^{9,21}$ Others employ cryogenic technology, bipolar RF energy,$^{10,18,19,22}$ microwave energy,$^{23,24}$ or diode laser energy$^{25}$ to destroy endometrial tissue.

These treatment modalities generate extensive discussions in the gynecologic community worldwide regarding their compatibility with an office setting. Endometrial ablation in an office-based clinical practice is less of a challenge than rollerball method due to the fact that the techniques are less complex, appear to be as safe as or safer, and generally do not require expensive endoscopic videoequipment. A major factor, nevertheless, remains the amount of intraoperative and postoperative discomfort associated with each treatment method. The physician’s office can rarely accommodate administration of full, deep intravenous anesthesia, and most gynecologists are reluctant to perform the surgical procedure and simultaneously monitor the patient.

![Figure 5. Postoperative pain level: median visual analog scale values.](image-url)
FIGURE 6. Postoperative pain level: median numeric rating scale values.

FIGURE 7. Changes in PGF$_{2\alpha}$ values over time.
under intravenous sedation. In addition, many other issues, regulatory and legal, make in-office anesthesia undesirable. Lack of published data on the expected amount of intraoperative and postoperative pain associated with one treatment modality or another has also delayed introduction of endometrial ablation into the office. Information on anesthesia protocols (paracervical block, intravenous) that would be suitable for an office procedure does not exist. To the best of our knowledge, this clinical study represents the first serious attempt to assess and compare pain associated with two second-generation ablation technologies in a prospective, multicenter clinical trial.

The causal mechanism of the pain associated with endometrial ablation does not rest on a single factor. At least three factors may play a key role in promoting pain. First, distention of the uterine cavity can generate pain during and after the procedure. In this study, the ThermaChoice balloon catheter applied a distending pressure of 160 to 180 mm Hg to the uterine wall. In the NovaSure system suction is employed to engage endometrial tissue in permanent and close apposition to the electrode. Second, time of tissue exposure to the destructive element (heat) with the ThermaChoice system is 8 minutes compared with 1.5 minutes for NovaSure.

Finally, by-products of ablation may penetrate into myometrium and blood stream. Some biologically active substances released during tissue death (PGF$_{2\alpha}$) may interact with uterine muscle, causing cramping, and because they are lipid soluble they can pass easily through cell membranes. With the ThermaChoice system, ablation by-products are continuously directed into tissue by the pressurized balloon, which acts as an impermeable membrane. With the NovaSure system, these by-products are continuously evacuated from the uterine cavity by suction. It is possible that this trial did not measure this effect in serum samples due to the fact that PGF$_{2\alpha}$ is rapidly inactivated in the systemic circulation and inactive metabolites are excreted. This difference would probably be more evident if endomyometrial tissue samples were analyzed instead. It is also possible that other prostaglandins may be involved in generating cramps and nausea and vomiting in patients undergoing endometrial ablation.

Although no direct information regarding a comparison of intraoperative and postoperative pain associated with approved endometrial ablation systems is available, an indirect assessment on applicability of paracervical block plus intravenous sedation can be drawn from results of randomized, controlled trials conducted under the guidance of the Food and Drug Administration. In these studies the anesthesia regimen was left to the discretion of surgeons and patients, and the percentage of patients treated under paracervical block and intravenous sedation was reported (Figure 8). The fact that the highest percentage of patients using this anesthesia regimen were treated with NovaSure

![FIGURE 8. Local and intravenous sedation requirements in FDA trials.](image-url)
ablation may indicate that this modality has the potential to be used in an office setting. This was also suggested by our results. Nevertheless, required precautions must be observed with administration of intravenous drugs. The clinical office must have basic equipment not only to monitor the patient’s status, but also to overcome and treat complications.

It is also imperative to conduct thorough screening to identify women best suited for an office-based procedure, including basic information on the woman’s pain threshold. If she cannot tolerate a regular gynecologic examination, quite certainly she would be a poor candidate for office ablation and should be treated in a surgery center or operating room under general anesthesia. Proactive patient education also has a positive impact on the success of the procedure. Continuous communication with the patient during the procedure is important. If she is aware of the step the surgeon is about to perform, she will most likely respond in a compliant way.

Conclusion

The NovaSure system was associated with statistically significantly less intraoperative and postoperative pain, nausea, and vomiting than the TheraChoice system. The NovaSure procedure also requires shorter time to perform and therefore has a better chance of being accomplished successfully using PCB with or without intravenous sedation.

References


