



TITLE: Devices for Endometrial Ablation Therapy in the Outpatient Setting: Clinical- and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

Excessive menstrual bleeding or menorrhagia occurs in about 22% of premenopausal women and is a significant cause of morbidity in this population.¹ Clinically, menorrhagia is defined as a menstrual blood loss of more than 80 mL or as menstrual bleeding lasting longer than seven days over several consecutive cycles.^{1,2} From a patient perspective, menorrhagia can be extremely burdensome, interfering with work, social activities, hobbies and holidays, and can cause anxiety, depression, and embarrassment.² Importantly, menorrhagia is responsible for about one-third of hysterectomies in western countries.¹

Drug therapy with agents such as tranexamic acid, mefenamic acid, and hormones are often used as first-line treatments for menorrhagia.¹ In those who fail to respond to drug therapy, surgical options may be employed.¹ Hysterectomy has traditionally been considered the surgical treatment for menorrhagia and has a 100% success rate in achieving amenorrhea, the absence of menstruation.^{2,3} There are disadvantages to hysterectomy, however, such as physical complications and long recovery times.^{2,3} Endometrial ablation (surgical destruction of the endometrial lining of the uterus using electrical, thermal, or laser energy)^{2,4} is an alternative to hysterectomy in individuals with menorrhagia.⁴

The NovaSure and Gynecare Thermachoice are two devices that are used for endometrial ablation. NovaSure uses impedance controlled radio-frequency energy to destroy the lining of the uterus.⁵ The device consists of a radio-frequency controller and a disposable gold-plated, mesh electrode that conforms to the endometrial cavity.⁵ The electrode is inserted into the uterine cavity and suction from the system's generator is used to bring the endometrium into contact with the expanded mesh electrode.⁶ Energy from the controller then vaporizes the endometrium during a programmed treatment cycle that lasts 40 seconds to 120 seconds depending on endometrial thickness.⁴ The GyneCare Thermachoice system is comprised of a

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controller unit and a hand piece with a catheter that has a silicone balloon at its distal end.⁶ The catheter is inserted into the uterine cavity to the level of the fundus and then filled with 5% dextrose in water to achieve a pressure between 160 mm Hg and 180 mm Hg.⁶ The controller is activated to maintain pressure at 180 mm Hg and a temperature at 87 degrees Celsius for eight minutes, which destroys the endometrium.⁶ Currently, the Thermachoice III is the version being marketed and has greater depth of necrosis and better coverage at the extremes of the uterine cavity than previous versions.⁷ Both devices for endometrial ablation can be used on inpatient or outpatient populations.^{5,8}

For menorrhagia that is not treatable with medication, endometrial ablation may have some advantages over other treatment methods such as hysterectomy. It is less invasive and uses fewer health care resources, particularly when performed on an outpatient basis.² As well, outpatient endometrial ablation may include avoidance of general anesthesia and its associated risks, less time away from work and home, and elimination of an anesthetist and operating theatre costs.⁷ The purpose of this report is to review the evidence of clinical- and cost-effectiveness of the Thermachoice III and NovaSure systems for endometrial ablation in the outpatient setting. This information could potentially help in decisions about purchasing these technologies.

RESEARCH QUESTIONS:

1. What is the clinical-effectiveness of devices for endometrial ablation therapy used in the outpatient setting?
2. What is the cost-effectiveness of devices for endometrial ablation therapy used in the outpatient setting?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and May 2009. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs), controlled clinical trials, observational studies, and economic evaluations.

SUMMARY OF FINDINGS:

There were no relevant health technology assessments, systematic reviews, meta-analyses, or controlled clinical trials identified. One relevant RCT⁷, three observational studies,⁹⁻¹¹ and one economic evaluation were identified and included.¹² Five additional observational studies on the Thermachoice system were identified that used earlier versions of the technology and were not included in this report.¹³⁻¹⁷ The economic evaluation also used an earlier version of the Thermachoice system, but was included as there were no other economic evaluations identified.¹²

Randomized controlled trials

Marsh et al.,⁷(2007) conducted an RCT to evaluate outpatient versus daycase endometrial ablation using the Thermachoice III device. The definition of a daycase patient was not given in the report, but generally refers to a patient who is admitted electively to a hospital during the course of a day to undergo a procedure, but does not require a hospital bed overnight.¹⁸ An outpatient is not admitted to the hospital, but may need to use a bed for a specific short procedure taking an hour or less.¹⁸ The study was set in a large United Kingdom teaching hospital and included 73 women with menorrhagia (n=39 outpatient and n=34 daycase). Women were included if they had menorrhagia for at least six months, wished to avoid future pregnancy, and who had normal scans of the uterus, endometrial samples and cytology of the cervix. It was not explicitly stated whether or not all patients were premenopausal. Women with fibroids, polyps, or premalignant lesions, cavity lengths exceeding 12 cm, were pregnant, or had pelvic inflammatory disease (PID) were excluded. Patients were recruited from the gynecology department of the hospital and randomized to outpatient or daycase treatment.

Women in the outpatient arm took 800 mg of ibuprofen the evening before and one hour before the procedure. As well, during the procedure, they could have “rescue analgesia” with Entonox® (a mixture of 50% oxygen and 50% nitrous oxide) if needed, but no local anesthetic or sedation was given. For post-operative pain, they could have 50 mg to 100 mg of oral tramadol. Daycase patients were given a standard general anesthetic (propofol and inhalation gases, intraoperative fentanyl and rectal diclofenac). Postoperatively, they could have either tramadol or diclofenac. Endometrial ablation was performed with the Thermachoice III device by one of the investigators. The primary outcome of the study was an assessment of overall discomfort after undergoing treatment using visual analogue scales (VAS) and categorical pain-intensity Likert scales (with response options of none, mild, moderate, severe, or very severe) at discharge from hospital. Secondary outcome measures for both groups included an assessment of postoperative recovery (nausea and vomiting rates, total time spent in hospital, and the need for a postoperative overnight hospital stay). For outpatients, other secondary outcome measures included an assessment of intraoperative VAS pain scores and the need for rescue analgesia.

The average age of the study participants was 41.7 ± 5.35 in the outpatient group and 42.9 ± 6.36 in the daycase group. Ethnicity was not reported. The difference in mean overall VAS pain score was not statistically significant (59 mm; 95% CI: 50.6 mm to 67.6 mm for outpatients and 53 mm; 95% CI: 42.0 mm to 63.8 mm for daycase patients). As well, there were no significant differences between the Likert scale descriptions of overall discomfort, with the majority of women rating the pain as none to moderate. The proportion of women in the outpatient group who experienced nausea was significantly lower than in the daycase group (13% versus 65%, respectively, $p < 0.0005$). As well, those in the outpatient group were significantly less likely to use post-operative anti-emetics or experience vomiting and had significantly shorter times in the hospital (1 hour and 40 minutes versus 8 hours 12 minutes for the daycase group, $p < 0.005$). For outpatients, intraoperative pain scores remained below 45 mm throughout treatment and 36% required rescue analgesia, however, five of the 39 patients in this group requested that the procedure be stopped due to pain. The use of rescue analgesia in these five women was not reported. The authors concluded that outpatient Thermachoice III could be performed in most women and resulted in similar pain as daycase treatment with significantly less nausea, vomiting, need for antiemetics, and time spent in hospital. The authors did express concern, however, about an unpredictably wide range of intraoperative and overall pain scores in both groups (i.e., from “no pain” to “worst imaginable pain”).

Limitations to this study included its small sample size and short duration of follow-up for outcomes. The generalizability of this study may have been limited by its small sample size. As well, it was unknown if the results were generalizable to women with larger uterine cavities, women with other excluded conditions or with previous versions of the Thermachoice device.

Observational studies

Samuel et al.,¹¹ (2009) performed a prospective cohort study to assess the NovaSure endometrial ablation system in the outpatient setting when used under local anaesthesia (n=18), compared to standard daycase procedure under general anaesthesia (n=20). The study was set in university teaching hospital. The study population consisted of all women who underwent endometrial ablation with the NovaSure between June 2005 and April 2006 to treat heavy menstrual bleeding refractory to medical therapy. All treatments were performed by a single surgeon. Patients chose which treatment setting they preferred. Specific inclusion and exclusion criteria were not given in the article. One surgeon performed or supervised all procedures. One hour before the procedure, outpatients were treated with 100 mg of rectal diclofenac (or tramadol if diclofenac was contraindicated), two tablets of oral co-dydramol (a combination of 10 mg of dihydrocodeine tartrate and 500 mg of acetaminophen) and oral cyclizine 50 mg. A local anaesthetic was injected into the cervix. A designated nurse stayed with outpatients throughout the procedure to offer support and distraction. Daycase patients were given 100 mg of rectal diclofenac at the start of the procedure and general anaesthesia. Post-operatively, all patients recovered in a daycase ward bed and were given morphine 10 mg or codeine 30 mg to 60 mg as required. Patients were discharged once the pain was controlled, at least two hours after the last dose of opioid. Primary outcome measures included subjective self-assessment of uterine bleeding symptoms on a five-point scale (“no bleeding”, “spotting”, “light bleeding”, “moderate bleeding”, or “heavy bleeding”), improvement in bleeding symptoms (“much better”, “a little better”, “same”, or “worse”) and patient satisfaction with the procedure (“yes” or “no”). Secondary outcome measures included health-related quality of life (HRQL) measured on the menorrhagia multi-attribute utility assessment, and improvement in menstrual-related symptoms such as dysmenorrhoea and pre-menstrual syndrome. All outcomes were assessed with a questionnaire six months after treatment.

The average age of patients was 40.6 years (range: 26 years to 50 years) in the daycase group and 42 years (range: 32 years to 49 years) in the outpatient group. The groups did not differ in terms of demographic characteristics, but ethnicity was not reported. All procedures were successfully accomplished. The six month questionnaire was returned by 94% of the outpatient group, but by only 65% of the inpatient group. There were no significant differences between the outpatient and daycase groups for improvement in menstrual blood loss (94% versus 84% respectively, p=0.6), amenorrhoea rate (29% versus 46%, respectively; p=0.5), amenorrhoea or spotting rate (47% versus 62%, respectively; p=0.5), and satisfaction rate (82% versus 85%, p=1.0). As well, the difference in the proportion of patients who reported that they would recommend the treatment to a friend did not differ between treatment settings (88% for outpatients compared to 77% of daycase; p=0.7). When looking at the two groups combined, 90% (95% CI: 73% to 98%) women reported an improvement in menstrual bleeding symptoms and 37% (95% CI: 20% to 56%) achieved amenorrhoea. Overall, 83% (95% CI: 65% to 94%) of patients were satisfied with treatment. HRQL improved in all domains following treatment and differences between treatment settings were not statistically significant. The authors concluded that endometrial ablation for heavy menstrual bleeding with the NovaSure device was an effective, safe, and feasible treatment in both the outpatient and daycase settings and reported that a choice of treatment settings should be offered to this patient population.

There were a number of limitations to this study that relate to its design. First, women could choose their treatment setting and there could be systematic differences between women who chose one setting over the other. As well, the questionnaire was given six months after treatment which means there could be recall bias. It was not stated whether all patients were pre-menopausal so it was not clear whether the results would be generalizable to this group. As well, inclusion and exclusion criteria were not explicitly stated, making it difficult to determine to whom the results would be generalizable. While the fact that the same surgeon performed the daycase and outpatient procedures makes the two groups more comparable, it is unknown if similar outcomes could be achieved by a different surgeon who may not have the same level of skill or expertise.

Varma et al.,¹⁰ (2008) conducted a prospective observational study of the post operative rescue analgesia requirements and duration of hospital stay in women who underwent endometrial ablation with the Thermachoice III as either outpatients (n=51) or daycase patients (n=50). The study was set in a menstrual disorders clinic. The women who were included in the study were premenopausal, had heavy menstrual bleeding that was subjectively defined, and were referred by primary care or by a physician in the clinic. These women had been offered medical treatments for at least six months prior to the study commencing. Women were excluded if they had significantly sized uterine fibroids (fibroids greater than 3 cm size in any uterine location), uterine cavities greater than 10 cm in length, uterine cavities of abnormal shape, endometrial hyperplasia or cancer, or an active pelvic infection. One to two hours before the procedure, outpatients were treated with 100 mg of rectal diclofenac (or tramadol if diclofenac was contraindicated), two tablets of oral co-dydramol (a combination of 10 mg of dihydrocodeine tartrate and 500 mg of acetaminophen) and oral cyclizine 50 mg. A local anaesthetic was injected into the cervix. During the procedure a nurse provided continuous supportive care. Women in the daycase cohort were admitted to the hospital the day of the procedure and underwent general anesthesia. They also were treated with diclofenac 100 mg and 1 g acetaminophen rectally (or acetaminophen alone if diclofenac was contraindicated) just prior to performing the procedure. After the procedure all women recovered in a daycase bed and were allowed home after a minimum of two hours and were given post-procedure pain relief with diclofenac or co-dydramol. The main outcome measures for both cohorts were requirement for rescue analgesia and duration of hospital stay. As well, all patients assessed their pain on a VAS (0 to 10) immediately following the procedure.

The average age of study participants was 43.4 years (range: 29 years to 55 years). Ethnicity was not reported. Women in the outpatient cohort had significantly shorter hospital stays than women in the daycase cohort (11 hours; 95% CI: 9 hours to 13 hours compared to 17 hours; 95% CI: 14 hours to 20 hours). Outpatients had lower requirements of rescue analgesia. After adjusting statistically for confounders, however, there was no difference in duration of hospital stay or in the strength of rescue analgesia used. Pain scores of the VAS were not reported. From this, the authors concluded that duration of hospital stay with endometrial ablation was not entirely dependent on whether the procedure was performed on an outpatient or daycase basis.

Limitations to this study included its observational design, which could create confounding, although the authors did try to correct for this statistically. There were differences between groups in the proportion of women with reported dysmenorrhea and retroverted uterus, which could bias the results. As well, given that the study was nonrandomized, it was possible that the cohorts differed in their levels of pain tolerance, which could have led them to choose outpatient or daycase treatment. Finally, the authors reported that their study was likely underpowered. In terms of generalizability, it was not clear whether the results would be generalizable to women with fibroids or higher uterine cavity lengths.

Chapa et al.,⁹ (2008) performed a prospective single group observational study in 148 women to assess the tolerability of in-office endometrial ablation using the Thermachoice III, performed under local anesthetic. Premenopausal women aged 21 and over with dysfunctional menstrual bleeding for at least six months were recruited from a community-based obstetrics and gynecology clinic in the United States. These women had been treated with medical therapies for at least three months or had refused medical management and preferred not to have a hysterectomy. Patients were excluded if they had endometrial hyperplasia or another endometrial malignancy, fibroids greater than >4 cm in dimension, were post-menopausal, or desired to be fertile in the future. Patients were given oral nonsteroidal anti-inflammatory drugs (NSAIDs) 48 hours prior to the procedure and were treated 20 minutes to 30 minutes before the procedure with intramuscular ketorolac, hydrocodone/acetaminophen, promethazine, and alprazolam in addition to local anesthetic. The primary outcome measure of the study was tolerability and pain within the first 24 hours following the procedure which was measured with four items including the need to stop the procedure due to pain, need for reinjection of the local anesthetic, need for admission due to pain, and overall pain experience in the first 24 hours measure on a 10 –point VAS. Adverse events in the first two weeks following treatment were assessed as a secondary outcome measure.

The average age of study participants was 41 years (range: 29 years to 48 years) and 69% were Hispanic. Of the 148 patients enrolled, 143 completed the two-week follow-up. There were no instances where the procedure had to be stopped due to pain and no admissions due to pain. One patient required more local anesthetic to be injected during the procedure. The average pain score on the VAS during the procedure was two out of 10 and ranged from one to three. The highest level of post-procedure pain on the VAS was reported within six hours (mean = 5.0; range 3 to 7) and was mainly categorized as cramping and pressure. The most common reported adverse events in the first two weeks were bacterial vaginosis (11% of patients) and post-procedure pelvic pain (5.6%). Ninety percent of patients reported being very satisfied with the procedure and the remaining 10% reported being satisfied with the procedure. The authors concluded that endometrial ablation could be performed in the physician's office under local anesthesia, with high tolerability and satisfaction.

The major limitation to this study was the lack of a comparator. As well, it was not clear if all procedures were performed by the same physician. The level of experience and training of the individual performing the procedure could affect generalizability of the results. As well, it was not known whether similar results would be obtained if a different protocol for patient control and anesthesia was used. The authors felt that they may have had better post-operative pain relief if a longer acting local anesthetic was used. Finally, it was not clear if the results would be generalizable to other populations given that the majority of patients were Hispanic.

Economic evaluations

Brown et al.,¹² (2006) conducted a cost-effectiveness analysis comparing levonorgestrel intrauterine system (LNG-IUS) and endometrial ablation using the Thermachoice device for the treatment of heavy menstrual bleeding. The LNG-IUS is a device that is inserted into the uterus and releases 20 µg levonorgestrel each day.¹⁹ Data for the cost-effectiveness analysis were obtained from an open-label randomized trial that was conducted in a hospital-based menstrual disorders clinic in New Zealand.¹⁷

The study population included 79 women with heavy menstrual bleeding who were randomized to the LNG-IUS (n=40) or Thermachoice (n=39) for outpatient treatment. It was not clear

whether or not these women were pre-menopausal, but likely were given that the study included women with self-described heavy menstrual bleeding and discrete episodes of menstruation occurring every three weeks to six weeks.¹⁷ A decision tree model was developed using data from the study. The model included direct and indirect medical costs, which consisted of treatment, subsequent medical procedures, lost income, and subsequent medical treatment for failed procedures. Some of these costs (visits to general practitioners, missed workdays, and medication usage) were determined from patient estimates. The model did not include costs associated with pretreatment consultations as these were assumed to be equal between groups. It was also assumed that 25% of women who fail treatment would require hysterectomies. The model also considered changes in quality of life and probabilities for each outcome to calculate the incremental cost-effectiveness of the treatments. Health-related quality of life was measured with the Short Form-36 (SF-36) and the change in this measure was calculated between baseline and 24 months following the procedure. A sensitivity analysis was also performed to determine whether the results were robust to changes in model inputs. The costing year of the study was 2004 and costs were determined in New Zealand and US dollars. A 5% discount rate was used.

The model showed that the expected cost of treatment was NZ\$1241 (US\$869) for the LNG-IUS and NZ\$2418 (US\$1693) for endometrial ablation with Thermachoice. Over the 24 year period the SF-36 scores improved by 15 points with the LNG-IUS and 12 points for Thermachoice, but it was not reported whether this difference was statistically significant. Incremental cost-effectiveness ratios were not reported. From sensitivity analysis it was determined that the results were robust to a 25% decrease in the price of the primary cost drivers and to changes in the rates of failed treatment. From this, the authors concluded that LNG-IUS would appear to be cost-effective when compared with the Thermachoice for treatment of heavy menstrual bleeding.

This economic evaluation had a number of limitations. The study from which cost and HRQL data were obtained had a small sample size that was perhaps not generalizable to the larger population with menorrhagia. Further, this study did not limit enrollment to patients who had failed medical therapy (other than LNG-IUS), which may not make it consistent with practice. Another limitation that the model was based upon some cost data which were patient reported which may or may not be accurate. Moreover, the difference in change in SF-36 scores was small. The statistical significance of this difference was not reported and clinical importance was not discussed. Finally, given that an earlier version of the Thermachoice was used, it is not clear if the results would be generalizable to the present device. It is also unclear whether costs from New Zealand would be generalizable to the Canadian population.

Limitations

There was one RCT⁷ that evaluated Thermachoice III specifically in the outpatient setting and this trial was relatively small and mainly reported on short-term outcomes including pain control and post-operative recovery. Unfortunately, longer term outcomes such as amenorrhea or decrease in menorrhagia were not assessed in this study. Moreover, there was no identified RCT that assessed the clinical-effectiveness of the NovaSure device.

For both devices, evidence of clinical-effectiveness in the outpatient setting was generated from a few observational studies⁹⁻¹¹ that were relatively small in size and prone to bias and confounding. This may be particularly true of one study where patients were permitted to select their preference for treatment setting.¹¹ Although, even with the study investigators selecting the

treatment setting, there could be systematic differences in patients assigned to each treatment.^{9,10}

Overall, the four identified studies provided limited information of clinical effectiveness in terms of feasibility of use of the two devices in three different settings (i.e., daycase, outpatient, office) and under specific protocols for pain control (local anesthetic, general anesthetic, or no anesthetic). One study reported on longer-term outcomes and success rates.¹¹ Further, generalizability of the results may be limited in that similar results may not be observed with different surgeons or gynecologists operating the devices, or under different protocols for pain control. Importantly, the studies excluded women with a number of gynecological problems, so the results may not be generalizable to women with such conditions. However, women with such conditions may not be suitable candidates for the procedure any way.

Finally, evidence of cost-effectiveness was limited as there was only one study identified which may not be generalizable to the Canadian health care system or to the most current Thermachoice device. No cost-effectiveness studies were found on the NovaSure device.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Overall, endometrial ablation was well tolerated in terms of pain in the outpatient and daycase settings with relatively few complications with either device. In the absence of local anesthetic, however, the procedure had to be stopped in a minority of women⁷ and there was a large and unpredictable variation in the amount of pain reported. One study suggested that endometrial ablation with the Thermachoice III may be a feasible alternative in the office setting. With endometrial ablation using the NovaSure device, limited evidence suggested that its success rate in the outpatient setting was acceptable. These observations are, however, based on a small number of studies with important limitations. There were no head-to-head comparisons between the Thermachoice III and NovaSure devices in the outpatient setting, so it is not possible to make any conclusions about their comparative clinical- or cost-effectiveness.

Given the lack of good quality or generalizable economic evidence, conclusions about the cost-effectiveness of either device in the outpatient setting cannot be made.

There is insufficient clinical or economic data to suggest one device over the other when making a purchasing decision, but outpatient endometrial ablation with either device seems clinically feasible under specific protocols for pain control. Evidence of economic feasibility in the outpatient setting is lacking.

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