Evaluation of HydroThermAblator and Rollerball Endometrial Ablation for Menorrhagia 3 Years after Treatment

Milton H. Goldrath, M.D.
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Abstract

Study Objective. To compare the safety and efficacy of endometrial ablation using HydroThermAblator (HTA) and rollerball (RB) for treatment of menorrhagia.

Design. Prospective, randomized, multicenter study (Canadian Task Force classification I).


Patients. Two hundred seventy-six women.

Intervention. Hysteroscopic endometrial ablation with the HTA (187 women) and RB (89).

Measurements and Main Results. Bleeding was assessed by pictorial diaries for 12 months, with patient interviews at 24 and 36 months. Amenorrhea rates, reduction of bleeding to normal levels or less, and patient satisfaction were tracked for 36 months, with rates in the HTA group of 53%, 94%, and 98% and in the RB group of 46%, 91%, and 97%, respectively.

Conclusion. Endometrial ablation with the HTA is a safe, effective, and durable treatment of menorrhagia in a broad patient population. It offers advantages over RB by reducing anesthesia requirements, reducing operating time, and eliminating risks of excessive fluid absorption, and is more easily learned.

Menorrhagia is a significant clinical problem for premenopausal women, accounting for millions of visits annually to gynecologists in the United States. Often patients are provided relief through medical therapy; however, hysterectomy is the final solution for many women.

Although the minimally invasive alternative of hysteroscopic endometrial ablation has been available for 2 decades, it is estimated that at least 25% of hysterectomies performed are to relieve excessive menstrual bleeding from benign causes. This is due in part to the high technical proficiency necessary to perform resectoscopic ablation, and to failure of some global techniques to achieve a high rate of amenorrhea. In addition, even the skilled hysteroscopic surgeon must remain vigilant with regard to the risk of absorption of excessive amounts of nonphysiologic solutions used to maintain working space within the uterine cavity during resectoscopic procedures.

In an effort to overcome the level of proficiency required to treat the entire uterine cavity safely and effectively by traditional hysteroscopic ablation techniques, the HydroThermAblator (HTA) system (Boston Scientific, Natick, MA) was developed. A multicenter, randomized, phase III clinical trial with 1-year follow-up was conducted as a requirement for receipt of Food and Drug Administration (FDA) approval of the system in the United States. This report extends the follow-up of clinical outcomes from the study of these patients to 3 years.

Materials and Methods

This randomized study was designed to evaluate the safety and efficacy of endometrial ablation with the HTA system compared with traditional hysteroscopic rollerball technique. Institutional review board approval was obtained. Patients were screened at 9 centers by 14 investigators to determine if they satisfied inclusion criteria: age 30 to 50 years, childbearing completed, history of at least 3 months of excessive bleeding documented by a pictorial bleeding assessment chart (PBAC), uterine cavity measuring between 4 and 10.5 cm, and failed, not tolerated, or refused medical therapy. Exclusion criteria were active or symptomatic pelvic inflammatory disease, intramural myomas greater that 4 cm, submucosal myomas or polyps, and fully septate uterus.

All patients had an endometrial biopsy and cervical cytology to rule out hyperplasia and malignancy. Those who met inclusion criteria were randomized by computer-generated block on a 2:1 basis (HTA: rollerball), and received...
a single injection of depot leuprolide acetate 7.5 mg on day 21 ± 2 of their cycle. Treatment was scheduled between 19 and 27 days later, provided menses had ensued.

Based on an estimate of successful reduction of excessive menstrual bleeding to normal levels or less in 80% of women treated by rollerball ablation, it was determined that a sample of 276 subjects was required to demonstrate equivalence if the success rate in the two groups did not differ by more than 20%. Other assumptions were a two-sided $\alpha$ of 5%, power of 90%, and dropout rate of 12%, all within the 2:1 ratio of HTA versus rollerball. Choice of treatment setting (office-outpatient surgery center, hospital operating room) and anesthesia regimen (paracervical block alone or with intravenous sedation, general inhalation anesthesia) were decided mutually by patient and physician. The primary end point of the study at 12 months after treatment was reduction of PBAC scores to 75 or less (established by the FDA) between HTA treatment group and the control group (rollerball). A quality of life questionnaire was administered for pretreatment and posttreatment secondary analyses. Patients visited the treating physician for follow-up 2 weeks and 3, 6, and 12 months after treatment. Further follow-up was done at 2 and 3 years after treatment through interviews if patients were not examined.

The HTA Device

The HTA system is described elsewhere. Its control mechanisms are housed in a compact console mounted on a mobile cart (Figure 1). Circulation of fluid (0.9% saline solution) is controlled by gravity, based on the height of the fluid container above the patient’s uterus, with actual intrauterine pressure reduced from hydrostatic pressure by the effect of the evacuation pump that recirculates fluid to the elevated reservoir. The fluid reservoir, mounted on the unit’s dedicated intravenous pole, is adjusted to a height of 115 cm (45 inches) above the patient’s uterus to provide a net intrauterine pressure in the range of 50 to 55 mm Hg, well below the minimum pressure of 70 mm Hg required to open the fallopian tubes. With the operating table at a typical height for hysteroscopic procedures, and with an average-size patient, the uterus is approximately 85 cm (34 inches) above the floor. The fluid reservoir may be elevated to a maximum height of 221 cm (87 inches) above the floor when the connecting tubing set is fully extended. Consequently, maximum net intrauterine pressure obtainable during HTA treatment is less than 70 mm Hg.

After the cervix is dilated to accept the insulated hysteroscopic sheath (7.8 mm outer diameter; Figure 2), which accommodates hysteroscope telescopes 3 mm or smaller, flow of room-temperature saline is started to allow visualization of the cervical canal and uterine cavity. As a safety feature, the HTA system is calibrated to detect loss of as little as 10 ml of saline from closed-loop circulation, so care is taken to not overdilate the cervix to ensure a good seal. Diagnostic hysteroscopy is performed with the HTA sheath to ensure absence of unrecognized pathology, and to identify the tubal ostia as landmarks indicating that the sheath has not been placed in a false passage. Only then is heating of circulating saline begun, with a therapy cycle of 10 minutes. On completion of the therapy cycle, the operator is prompted to wait for the 1-minute cooling cycle to finish, followed by a prompt that the sheath may be removed from the patient. Hysteroscopic visualization is maintained
throughout the procedure, allowing full appreciation of blanching caused throughout the cavity, even in the presence of cavity asymmetry.

**Results**

Of 276 women originally randomized, 269 received at least partial treatment. Complete treatments under the protocol were received by 177 patients in the HTA group and 85 in the rollerball group. Of seven incomplete HTA treatments due to technical difficulties with the device, three were converted to rollerball treatment. More patients underwent HTA (41%) than rollerball treatment (22%) in the office setting; one site had a fully equipped operating room. Similarly, more patients received local anesthesia, with or without sedation, for HTA (45%) than for rollerball treatment (22%). These factors contributed to the median time spent in the recovery room for the HTA group of only 70 minutes.

Intraoperative adverse events were limited, with two cervical lacerations (2.4%) in the rollerball group and two external burns (1.1%) in the HTA group. These burns, one on the buttocks and one on the upper thigh, were due to prolonged contact with the tubing that carries heated saline from the control unit to the hysteroscopic sheath; an insulating cover has been added to this tubing to eliminate the problem from the commercial version of the device. One of two women with cervical lacerations in the rollerball group developed a serious complication; 1 day after ablation she experienced fever, nausea, vomiting, and diarrhea and was admitted to the hospital. Laboratory tests indicated gram-negative septicemia. The woman responded to antibiotic therapy and was discharged 6 days later.

Postoperatively, three women had endometritis (HTA 2, rollerball 1), seven had urinary tract infections (HTA 5, rollerball 2, 2.4%), and seven had hematomata (HTA 2, 1.1%; rollerball 5, 5.9%) that was resolved by cervical dilatation during an office visit. During the 2-week follow-up visit at four of the nine investigational sites, changes in the appearance of cervical epithelium were noted during examination of 13% of HTA-treated patients, although no patients reported symptoms. These changes were thought to be related to thermal effects of HTA treatment; one investigator accounted for 48% of the observations. No mediators of symptoms were given to any of these patients, and in every case the cervix appeared normal at the 1-month visit. The two women in the HTA group with hematomata were not among these patients.

At 1 year, 12 patients who had received complete treatment were lost to follow-up, 10 (5.6%) from the HTA group, including 2 accidental deaths unrelated to surgery, and 2 (2.4%) from the rollerball group. Two patients in the HTA group had hysterectomies during the first year, which provided a per protocol population of 250 patients (167 HTA, 83 rollerball) at 12 months. At 2 years, the per protocol population was 220 patients (151 HTA, 74 rollerball), and overall, 203 (77%) of the original 262 patients treated per protocol (135 HTA, 68 rollerball) were available for evaluation of clinical efficacy data at 3 years (Table 1).

Pretreatment PBAC diary scores ranged from 143 to 8662 (mean 596.6 ± 787.6) for the HTA group and from 151 to 4140 (mean 585.5 ± 565.2) for the rollerball group. At 12 months, 40% (66/167) of the HTA group had scores indicating no bleeding-amenorrhea (PBAC zero) compared with 51% (42/83) of the control group. Bleeding was reduced to the FDA-mandated PBAC diary score of 75 or lower as the indicator of treatment success for comparison in 77% (128/167) and 82% (68/83) of HTA and rollerball groups, respectively. Normal bleeding, as indicated by a PBAC score of 100 or below, was achieved by 82% of HTA and 85% of rollerball patients (Table 2). At 24 months, complete elimination of menstrual bleeding (amenorrhea) was reported by 46% (70/151) and 46% (34/74) of women, respectively. Reduction of bleeding to normal levels or less was reported by 92% (139/151) and 92% (68/74), respectively. Results at 36 months were consistent with those at 24 month; amenorrhea in 53% (72/135) of HTA patients and 46% (31/68) of rollerball patients (Figure 3). Further consistency is shown in reduction of bleeding to normal levels or less of 94% (127/135) and 91% (62/68), respectively (Figure 4). In addition, 98% of HTA patients and 97% of rollerball patients reported satisfaction with treatment at 36 months.

Hysterectomies, repeat ablations, and other interventions for bleeding were tracked for 3 years. Hysterectomies were performed on 16 (9%) of 177 women in the HTA group and 5 (6%) of 85 women in the rollerball group, repeat ablations were performed on 3 (2%) and 3 (4%), respectively, and uterine artery embolization for myomas in 2 (1%) HTA patients. Reasons for hysterectomy were available for 10

### TABLE 1. Sequence of Patients Dropped from Study

<table>
<thead>
<tr>
<th>Reason</th>
<th>12 Months</th>
<th></th>
<th>24 Months</th>
<th></th>
<th>36 Months</th>
<th></th>
<th>Totals a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HTA</td>
<td>RB</td>
<td>HTA</td>
<td>RB</td>
<td>HTA</td>
<td>RB</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>2</td>
<td>0</td>
<td>10 a</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>17 a</td>
</tr>
<tr>
<td>Repeat ablation</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Lost</td>
<td>6 a</td>
<td>2 a</td>
<td>9</td>
<td>7 a</td>
<td>5</td>
<td>5</td>
<td>18 a</td>
</tr>
<tr>
<td>Totals</td>
<td>10</td>
<td>2</td>
<td>19</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>42 a</td>
</tr>
</tbody>
</table>

HTA = HydroThermAblator system; RB = rollerball.
aOverall totals reflect adjustment of earlier accounting errors and return of patients at 24 and 36 months.
patients: persistent pain (5), menorrhagia (3), benign pelvic mass (1), and endometriosis (1). Pretreatment PBAC scores (range 173–2370, median 490), age (range 30–50 yrs, median 40 yrs), and body mass index (range 17–45.8 kg/m², median 29 kg/m²) had no predictive value for final outcome. Overall success, considering women with normal bleeding or less and without repeat ablations, hysterectomies, or other interventional procedures, through 36 months of follow-up was 81.4% (127/156) for HTA and 81.6% (62/76) for rollerball.

**Discussion**

As with data for 1-year outcomes, analysis of outcomes at 3 years supports the conclusion that endometrial ablation performed with the HTA system is equivalent in efficacy to rollerball ablation. This is true for both patients whose menstrual bleeding was eliminated (amenorrhea) as well as for those whose bleeding was reduced to normal levels or less. In addition, the long-term stability of outcomes of HTA was achieved by physicians with only modest experience with the system. This is in contrast to the considerable experience with rollerball technique they brought to the study.

Reduction in Janssen diary scores and amenorrhea rates are the most objective basis for comparison of treatment outcomes, but analysis of responses to a quality of life assessment questionnaire provides a view of a patient’s sense of well-being and satisfaction with treatment. These questionnaires were completed by patients before and 12, 24, and 36 months after treatment. Both groups had essentially similar improvements regarding duration and regularity of menstruation, cycle interval, and interference with work, leisure pursuits, sexual activity, and the need to be confined to bed. Before treatment, 58.5% of the HTA group and 67.5% of the rollerball reported heavy bleeding of 4 days’ duration or longer. Such heavy bleeding was reported by 8%, 6.2%, and 4.4% of the HTA group at 12, 24, and 36 months, and by 8.8%, 2.8%, and 3.7% of the rollerball group, respectively. In addition, menstrual bleeding was reported to interfere with work and other normal activities by 89.6% and 90.3% of the HTA and rollerball groups.

**TABLE 2. Menstrual Status at 12, 24, and 36 Months**

<table>
<thead>
<tr>
<th>Menstrual Status</th>
<th>12 Months % (no.)</th>
<th>24 Months % (no.)</th>
<th>36 Months % (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HTA (n = 167)</td>
<td>RB (n = 83)</td>
<td>HTA (n = 151)</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>40 (66)</td>
<td>51 (42)</td>
<td>46 (70)</td>
</tr>
<tr>
<td>Normal</td>
<td>82 (137)</td>
<td>85 (71)</td>
<td>92 (139)</td>
</tr>
<tr>
<td>Excessive</td>
<td>18 (30)</td>
<td>15 (12)</td>
<td>8 (12)</td>
</tr>
</tbody>
</table>

HTA = HydroThermAblator system; RB = rollerball.

**FIGURE 3. Amenorrhea rates at 12, 24, and 36 months.**
(Figure 5), with over half of women in both groups losing at least 1 day of work a month. After treatment, 84.9%, 89.0%, and 91.2% of HTA group and 97%, 88.8%, and 92.6% of the rollerball group reported that menstrual bleeding had no effect at all on work or other normal activities at 12, 24, and 36 months; only 6.8%, 5.5%, and 5.1% versus 3.0%, 2.8%, and 5.6% reported continuing loss of work due to menstrual bleeding at 12, 24, and 36 months. These changes in significant lifestyle issues support satisfaction with HTA and rollerball treatment as reported by 98% and 96% of women, respectively, 36 months after treatment (Figure 6).

As with all procedures, the physician should appreciate certain nuances before performing HTA to ensure maximum safety and effectiveness. The cervix should be carefully dilated to avoid having fluid leak around the hysteroscope sheath. This translates to dilatation up to but not beyond 8 mm (24F). An additional tenaculum can be applied at either the 3 or 9 o’clock position after the tip of the sheath is positioned in the lower uterine segment, just inside the internal cervical os. This is in addition to the tenaculum typically applied at 12 o’clock to stabilize the cervix and provide countertraction while introducing instruments. An effective cervical seal can be accomplished even in women with a patulous cervix. After FDA approval for marketing of the HTA system, clinical users reported placement of an EndoLoop (Ethicon EndoSurgery, New Brunswick, NJ) around the patulous cervix before introducing the HTA.
sheath. The suture loop is tightened after the sheath is positioned and before starting fluid heating to provide an effective seal, allowing the procedure to be completed uneventfully. A vaginal speculum should be kept in position throughout the procedure to allow observation of the junction of the sheath with the cervix.

Initial concerns about a risk of heated saline escaping from the fallopian tubes and causing injury are mitigated by the HTA system’s low-pressure fluid delivery and fluid volume monitoring, and no such occurrence was observed during this trial or reported in over 10,000 HTA procedures performed worldwide. The HTA procedures performed during this trial under local anesthesia alone or with sedation (45%) support the conclusion that the lining of the uterus is insensitive to heat, and that the low pressure used causes little stretch receptor activity. The key to patient tolerance of HTA treatment with minimal anesthesia is effective administration of a paracervical block, followed by an adequate pause for the anesthetic to take effect before dilating the cervix. Pretreatment with nonsteroidal analgesics is common, but no data exist comparing this with placebo controls.

Because circulating heated saline delivers heat to target tissue, it contacts the entire lining of the uterine cavity. This implies that heat can be effectively delivered to all areas in an asymmetrically shaped uterine cavity, or in a cavity distorted by moderate-size myomas, providing both tubal ostia are visible on hysteroscopic examination. As such, it would be anticipated that HTA treatment might be a more effective choice for such patients, in contrast to a tissue-heating mechanism that requires direct contact with the surface of a fixed-shape device. Because fluid is recirculated at a rate of approximately 300 ml/minute, its therapeutic temperature within the cavity is easily maintained. Although uterine volume typically ranges from 10 to 30 ml, variations to even 60 ml present no technical limitation for the HTA system’s heating capabilities, and were not a reason for limiting uterine sounding depth to 10.5 cm in this study.

Long-term follow-up is important to document the stability of the results and to indicate that this is not just a short-term respite from hysterectomy. The 5-year follow-up in the thermal balloon study showed this, although there were subtle differences in patient population and inclusion criteria compared with this study.6

Conclusion

Long-term follow-up shows that HTA endometrial ablation can be performed safely and effectively by physicians with minimal experience. The technical proficiency necessary to perform the procedure can be gained easily and quickly, as indicated by 10 of the 14 investigators whose first HTA procedures were performed in patients in this phase III trial, whereas the 4 other investigators had only limited experience gained during phase II trials. The only technical prerequisite is routine diagnostic hysteroscopy skill. The low rate of further treatment, repeat ablations or hysterectomy, supports the expectation that HTA endometrial ablation can result in a considerable reduction in the costs of caring for patients with menorrhagia. Long-term results of HTA endometrial ablation are consistent with results obtained from expertly performed rollerball ablation.

The following clinical investigators participated in this study:

M. Weisberg, Philadelphia, PA; J. Berman, Novi, MI; P. Brooks, Los Angeles, CA; J. Cooper, Phoenix, AZ; R. Gimpelson, Chesterfield, MO; A. Greenstein, Novi, MI; R. Houck, Phoenix, AZ; D. Iddenden, Philadelphia, PA; J. Krotec, Philadelphia, PA; F. Loffer, Phoenix, AZ; B. Love, Montgomery, AL; A. Luciano, New Britain, CT; R. McCorvey, Montgomery, AL; and F. Sauer, New Britain, CT.
References


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