

Cervical Priming Prior to Operative Hysteroscopy: A Randomized Controlled Study Comparing the Efficacy of Laminaria versus Evening Primrose Oil*

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Objectives: To compare the efficacy of Laminaria versus Evening Primrose Oil as cervical ripening agent prior to operative hysteroscopy.

Materials and Methods: A randomized controlled trial carried out in a university hospital from April to August 2015. The Laminaria group patients received a single intracervical Laminaria tent (2 - 3 mm in diameter) 12 hours prior to the hysteroscopic procedure. The Evening Primrose Oil group of patients received 6 intravaginal Evening Primrose Oil capsules inserted into the posterior fornix 6 hours prior to the procedure followed by another 4 capsules inserted 1 hour prior to the procedure.

Results: Both Laminaria and Evening Primrose Oil were effective in dilating the cervix, but the initial cervical dilatation was significantly greater for the Laminaria group. The median duration of time needed to insert the 10mm Hegar's dilator was significantly longer for the Laminaria tent group, compared to the Evening Primrose Oil group (123 seconds vs 55 seconds, P-value 0.01). The ease of cervical dilatation was likewise significantly better for the Evening Primrose Oil group (26.19% vs 16.67%, P-value 0.04)

Conclusion: Both Evening Primrose Oil and Laminaria were effective in dilating the cervix. However, Evening Primrose Oil resulted in easier and faster cervical dilatation required for hysteroscopy. Evening Primrose Oil had better patient acceptability because it was more convenient and easier to use, and is less expensive, compared to Laminaria tents. Therefore, Evening Primrose Oil capsules is an easy-to-use regimen that can be recommended for patients undergoing operative hysteroscopy, to facilitate easier and faster cervical dilatation, and reduce complications associated with resectoscope entry.

Key words: operative hysteroscopy, cervical priming, laminaria tents, evening primrose oil

Introduction

Operative hysteroscopy has gained popularity as a minimally invasive approach to intrauterine lesions.¹ Hysteroscopy permits full visualization

of the endocervix, endometrial cavity, and proximal tubal ostia. It is helpful in diagnosing focal lesions that are missed with endometrial sampling.

However, despite the high efficacy of the procedure, both as a diagnostic or therapeutic tool, hysteroscopy may be associated with certain complications.² The incidence of these complications is low, 1–1.5%. Almost 50% of the complications are related to insertion of the

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hysteroscope or to the dilatation of the cervical canal.³ Common complications encountered during hysteroscopy include cervical tears, creation of false tracks and uterine perforation. Several modalities for cervical ripening prior to hysteroscopy have been tried to facilitate an easier uncomplicated entry and minimize the risk of complications during the procedure.⁴

Ripening of the uterine cervix is related to changes in collagen, glycosaminoglycans, and collagen degrading activity. Connective-tissue biopsy specimens from the cervix of pregnant women have demonstrated that the concentrations of collagen, sulfated glycosaminoglycans, and hyaluronic acid are lower during the pregnant state.⁵ Prostaglandins are capable of inducing production of hyaluronic acid by cervical fibroblasts, causing increased hydration and alteration of the composition of glycosaminoglycan and proteoglycan.⁶ Prostaglandins promote the infiltration of leukocytes and macrophages into the cervical stroma. They induce specific degradative enzymes that cause the changes in the extracellular matrix that are associated with ripening of the cervix.⁷

Misoprostol is a prostaglandin E1 analogue used in labor induction. It is perhaps one of the most studied cervical ripening agents used prior to hysteroscopy. Intravaginal misoprostol resulted in a softer, more easily dilated cervical canal, which in turn decreased the number of women who required further mechanical cervical dilation prior to hysteroscopy.

On the other hand, laminaria tents, made from the stems of *Laminaria japonica* or *Laminaria digitata* (brown sea weed), are attractive natural substances that can cause cervical dilatation and are well tolerated.¹ They have been shown to be effective in priming the cervix and in reducing the frequency of inadequate cervical dilatation prior to operative hysteroscopy.⁸ In 1990, Townsend and Melkonian evaluated the use of Laminaria tents prior to hysteroscopy in 300 patients. There were no complications with the use of Laminaria such as infection or bleeding. Some patients, however, complained of mild lower abdominal discomfort similar to menstrual cramps. In all cases, laminaria resulted in mechanical dilatation

of the cervix, which facilitated the passage of the diagnostic and operative hysteroscopes.¹

Darwish, et al. (2004) compared the efficacy of Laminaria tents versus vaginal misoprostol prior to operative hysteroscopy. Both were equally effective in inducing proper cervical priming prior to operative hysteroscopy with minimal time of cervical dilatation. Nevertheless, misoprostol may be superior due to easy application, reduced cost, and patient convenience and acceptability.¹ The main disadvantage on the other hand is its prohibited use in the country.

Evening Primrose Oil (*Oenothera biennis*) is a commonly used alternative therapy and a rich source of omega-6 essential fatty acids. It is best known for its use in the treatment of systemic diseases marked by chronic inflammation as well as for mastalgia, menopausal and premenstrual symptoms, cervical ripening, and labor induction or augmentation.⁹ Evening Primrose Oil is generally well tolerated, with reported minor adverse effects including abdominal pain, indigestion, nausea, softening of stools and headaches.^{10,11,12}

The seeds of the Evening Primrose are rich in omega-6 essential fatty acids, including linoleic acid and gamma-linolenic acid. The therapeutic effects of Evening Primrose Oil are attributed to the direct action of essential fatty acids on immune cells as well as their indirect effect on the synthesis of eicosanoids (e.g. prostaglandins, cytokines, cytokine mediators).¹³ Omega-6 fatty acids are metabolized into arachidonic acid, which is a precursor for the production of prostaglandin E2, the latter is known to cause cervical softening and uterine contractions.

In the Philippines, three studies investigated the efficacy of Evening Primrose Oil as a cervical priming agent prior to hysteroscopy. In a case series done by Aquino and colleagues in 2011, the ease of cervical dilatation was determined in 6 postmenopausal and 2 nulligravid premenopausal women. Ease of cervical dilatation was observed in all patients given intravaginal Evening Primrose Oil 4 to 6 hours before diagnostic hysteroscopy (7mm diameter).¹⁴ In 2009, Tanangonan and Capco compared oral Evening Primrose Oil and placebo prior to operative hysteroscopy in 42 patients.

They found that the Evening Primrose Oil group required less time for cervical dilatation compared to the placebo group.¹⁵ Carreon and Tanangonan (2012), in a case series, compared oral Evening Primrose Oil and intracervical Dinoprostone gel in 9 patients and found both equally effective in inducing adequate cervical priming prior to operative hysteroscopy. Nevertheless, Evening Primrose Oil may be preferred due to its oral route, reduced cost, patient convenience and acceptability.¹⁶

This study aims to determine the efficacy of Laminaria versus intravaginal Evening Primrose Oil in priming the cervix prior to hysteroscopy.

Objectives

To compare the efficacy of Laminaria versus Evening Primrose Oil as cervical ripening agent prior to operative hysteroscopy.

Specific Objectives

1. To compare the ease of cervical dilatation to allow insertion of a 10mm Hegar's dilator prior to operative hysteroscopy after cervical priming with intravaginal Evening Primrose Oil capsule versus intracervical Laminaria tent.
2. To compare the ability of attaining a cervical dilatation of 10mm prior to operative hysteroscopy after cervical priming with intravaginal Evening Primrose Oil versus intracervical Laminaria tent.
3. To determine complications and adverse effects related to the use of Evening Primrose Oil or Laminaria.
4. To measure and compare the surgeon's acceptability of Laminaria versus Evening Primrose Oil.
5. To evaluate patients' acceptability of the cervical ripening agent used in terms of pain, discomfort or bleeding.

Materials and Methods

This is a two-arm randomized controlled trial carried out at the Philippine General Hospital

from April to August 2015. The study was approved by the Research Ethics Board.

The computation of the sample size was generated using G*Power v.3.1.9.2 statistical software. The number needed to treat (NNT) is 84, with the Laminaria and Evening Primrose Oil group allocated the same number of subjects (n = 42 subjects).

The study population consisted of all women admitted for elective operative hysteroscopy, between 19 to 65 years of age, with a closed cervix on internal examination on admission. Specific hysteroscopic procedures included polypectomy, myomectomy, resection of endometrial mass, resection of uterine septum, removal of intrauterine device and targeted endometrial biopsy. Patients with contraindication to hysteroscopy (pregnancy, pelvic inflammatory disease, uterus more than 12 weeks size), with a patulous cervix, with history of cervical surgery or incompetence, with proplapsed endometrial polyp or submucous myoma, who received GnRH agonists which can result in a firm cervix, and who are mentally incapacitated to give consent were excluded.

Informed consent was taken from every participant. The principal investigator explained the objectives and discussed the details of the research to each subject including possible complications. Data collected from each subject such as demographic, history and pre-operative details were entered into a computerized database matrix.

The selected patients underwent full history taking, thorough general and pelvic examinations, and transvaginal ultrasonography to determine the nature, site and extent of intrauterine lesions. Patients were randomly assigned to Group A or Group B by means of drawing lots.

The first group (Group A) of patients received a single intracervical Laminaria tent (2 – 3 mm in diameter) 12 hours prior to the hysteroscopic procedure. The patients were placed in the dorsal lithotomy position, where a sterile vaginal speculum was applied and the cervix sterilized using Povidone Iodine solution. The Laminaria tent was removed aseptically from its package and grasped from its proximal end where the string is attached using Ring forceps. It was inserted into

the cervical canal until it passed the internal os with the string resting in the vaginal vault for easy removal.

For second group (Group B), received intravaginal Evening Primrose Oil capsules inserted in the posterior fornix. Six capsules (1000mg per capsule) were inserted in the posterior fornix 6 hours prior to the procedure followed by another 4 capsules inserted 1 hour prior to the procedure. Strict aseptic technique was observed by using sterile gloves during insertion. The Laminaria tents and the Evening Primrose Oil capsules were provided by the investigator.

All patients were given regional anesthesia and the initial determination of cervical dilatation was performed after induction of anesthesia. Three senior fellows of the Section of Reproductive Endocrinology and Infertility with a comparable level of experience performed all hysteroscopic procedures.

In the operating room, the degree of initial cervical dilatation was assessed by the maximal caliber of Hegar's dilator inserted without resistance with the patient under regional anesthesia. The dilators were inserted in ascending order, starting with the smallest size dilator (1mm). The duration (in seconds) of subsequent cervical dilatation until the 10mm diameter was reached was timed and recorded. The ease of cervical dilatation was measured using 5-point Likert scale.

Cervicovaginal canal dilatation complications such as laceration, bleeding, perforation and post-operative pain were reported. Post-operatively, the subject was interviewed by the principal investigator on the acceptability of the cervical priming agent and was measured using 5-point Likert scale.

The participants were asked to have at least 2 outpatient follow-ups after discharge. During that time, a repeat speculum and internal examination as well as assessment of any late onset complications were made.

Statistical Analysis

Statistical analysis was performed using independent t-test for each of the demographic data while Chi-square test of association was used

for the hysteroscopic procedure performed, baseline internal examination on admission. Non-parametric data were analyzed using Mann-Whitney U test.

All tests of significance between the two groups were carried out at 95% confidence interval using Mann-Whitney test. All data gathered from patients and results obtained from this investigation were treated as confidential information, known only to the research team and patients involved.

Results

Eighty-four patients who fulfilled the study's inclusion criteria were randomized. The demographic data of the participants are presented in Table 1. Independent t-test was used for each of the demographic data and obstetric history while Chi-square test of association was used the hysteroscopic procedure performed, baseline internal examination on admission. Non-parametric data were analyzed using Mann-Whitney U test. The mean age for both groups are comparable, 40.45 ± 10.13 for the Laminaria group and 40.83 ± 10.14 for the Evening Primrose Oil group. More than half of the patients, 24 (57.14%) patients for the Laminaria group and 33 (78.57%) patients for the Evening Primrose Oil group, completed college level. Monthly income was also comparable, with majority of the patients earning P10,000 or above per month (24 [57.14%] for the Laminaria group and 32 [76.19%] for the Evening Primrose Oil group). On analysis, there was no significant difference between the demographic data of the two groups.

Table 2 shows the comparison of both groups in terms of parity, manner of delivery, history of curettage and menopausal status. There was a significant difference in the parity and manner of delivery between the groups (p-value 0.03 and 0.02 respectively). The Laminaria group consisted mostly of multiparas (87.14%) and delivered vaginally (61.90%). The Evening Primrose Oil group consisted of mostly of nulliparas (52.38%).

Table 3 is a frequency table of the indications for hysteroscopy for the two groups. Majority of the patients presented with abnormal uterine

bleeding (36.9% for the Laminaria tent group and 39.29% for the Evening Primrose Oil group). Endometrial polyp was the most common pathology associated with abnormal uterine bleeding for both groups (52.38% for the Laminaria tent group and 61.90% for the Evening Primrose Oil group).

Analysis showed that the indication for hysteroscopy between the Laminaria tent and the Evening Primrose Oil group did not differ significantly (p-value of 0.48). The causes of abnormal uterine bleeding (polyp and myoma) were similar for both groups (P-value 0.11) reflecting a well-distributed patient population.

Table 1. Demographic Data of the Participants.

Demographic Data	Laminaria (n = 42)	Evening Primrose Oil (n = 42)	P-value
Actual age in years	40.45±10.13	40.83±10.15	0.66
19-29 years	4 (9.52%)	3 (7.14%)	0.95
30-39 years	19 (45.23%)	20 (47.62%)	
40-49 years	12 (28.57%)	10 (23.81%)	
50-59 years	5 (11.90%)	7 (16.67%)	
≥60 years	2 (4.76%)	2 (4.76%)	
Estimated monthly income			0.06
< P 10,000	18 (42.86%)	10 (23.81%)	
P 10,000 and above	24 (57.14%)	32 (76.19%)	
Educational attainment			0.06
Elementary level	5 (11.90%)	6 (14.29%)	
High school level	13 (30.95%)	3 (7.14%)	
College level	24 (57.14%)	33 (78.57%)	

* Statistically significant: p-value < 0.05

Table 2. Obstetric History.

Obstetric History	Laminaria Group (n = 42)	Evening Primrose Oil Group (n = 42)	P-value
Parity			0.03*
Nulliparous	10 (23.81%)	22 (52.38%)	
Primipara	8 (19.05%)	6 (14.29%)	
Multipara	24 (57.14%)	14 (33.33%)	
Manner of Delivery			0.02*
SVD	26 (61.90%)	15 (35.71%)	
CS	5 (11.91%)	3 (7.15%)	
N/A	11 (26.19%)	24 (57.14%)	
History of curettage/uterine surgery			0.75
With	6 (14.29%)	5 (11.90%)	
Without	36 (85.71%)	37 (88.10%)	
Menopausal status			0.76
Premenopausal	6 (14.29%)	7 (16.67%)	
Post-menopausal	36 (85.71%)	35 (83.33%)	

* Statistically significant: p-value < 0.05

The type of hysteroscopic procedure performed is shown in Table 4. Hysteroscopic polypectomy was the most common procedure performed in the Laminaria (64.29%) and Evening Primrose Oil group (73.81%). No statistical significant difference was noted (p-value 0.08).

Shown in Table 5 are the baseline internal examination findings of the patients on admission. The cervix of the patients in the Laminaria group

had a soft consistency (66.67%) and midline in position (45.24%). On the other hand, the cervix of the patients in the Evening Primrose Oil group had a soft consistency (52.38%) and posterior in position (52.38%). On further analysis, there was no statistical significant difference between the two groups for both consistency and position of cervix (p-value 0.32 and 0.16 respectively).

Table 3. Chief complaint (indications for hysteroscopy).

Reason for Hysteroscopy	Laminaria (n = 42)	Evening Primrose Oil (n = 42)	P-value
Infertility	2 (2.38%)	2 (2.38%)	0.48
Displaced Intrauterine device	3 (3.57%)	1 (1.19%)	
Endometrial mass	-	2 (2.38%)	
Postmenopausal bleeding	6 (7.14%)	4 (4.76%)	
Abnormal uterine bleeding	31 (36.9%)	33 (39.29%)	
Submucous myoma	11 (26.19%)	5 (11.90%)	
Endometrial polyp	22 (52.38%)	26 (61.90%)	

* Statistically significant: p-value < 0.05

Table 4. Hysteroscopic procedure performed.

	Laminaria (n = 42)	Evening Primrose Oil (n = 42)	P-value
Hysteroscopic polypectomy	27 (64.29%)	31 (73.81%)	0.08
Hysteroscopic myomectomy	11 (26.19%)	6 (14.29%)	
Hysteroscopy-guided endometrial biopsy	1 (2.38%)	-	
Hysteroscopic resection of endometrial mass	-	4 (9.52%)	
Hysteroscopy-guided IUD removal	3 (7.14%)	1 (2.38%)	

* Statistically significant: p-value < 0.05

Table 5. Baseline internal examination on Admission.

Internal Examination Upon Admission	Laminaria (n = 42)	Evening Primrose Oil (n = 42)	P-value
Consistency			0.32
Soft	1 (2.38%)	3 (7.14%)	
Medium	13 (30.96%)	17 (40.48%)	
Firm	28 (66.67%)	22 (52.38%)	
Position			0.16
Anterior	8 (19.05%)	3 (7.14%)	
Mid-position	19 (45.24%)	17 (40.48%)	
Posterior	15 (35.71%)	22 (52.38%)	

* Statistically significant: p-value < 0.05

As shown in Table 6, clinical characteristics between the two groups were analyzed using Mann-Whitney test. The mean initial cervical dilatation was 6.29 mm for the Laminaria group and 5.55mm for the Evening Primrose Oil group. The results showed that initial cervical dilatation between the two groups were statistically significant (P-value of 0.04), the initial dilatation being greater for the Laminaria group.

The median duration of time needed to insert the 10mm Hegar's dilator was 123 seconds for the Laminaria tent group and 55 seconds for the Evening Primrose Oil group. The difference was statistically significant with a p-value of 0.01.

The cervical dilatation was easy for the Laminaria tent group (16.67%) and very easy for the Evening Primrose Oil group (26.19%). The difference between groups was statistically significant with a P-value of 0.04.

Minimal cervical laceration occurred in 1 patient in the Laminaria tent group and 3 patients in the Evening Primrose Oil group. A p-value of 0.31 using Chi-square test denotes that the presence of such complication was not statistically significant.

Table 7 shows that majority of the patients randomized to the Laminaria tent group experienced mild pain during insertion while the

Table 6. Technical Characteristics.

	Laminaria (n = 42)	Evening Primrose Oil (n = 42)	P-value
Cervical dilatation (in mm)	6.29±1.66	5.55±1.73	0.04*
Time to Hegar's 10mm (in seconds)	123 (281)	55 (202)	0.01*
Ease of dilatation	4 (2)	5 (1)	0.00*
Very Difficult	5 (5.95%)	2 (2.38%)	0.04*
Difficult	6 (7.14%)	3 (3.57%)	
Good	8 (9.52%)	4 (4.76%)	
Easy	14 (16.67%)	11 (13.10%)	
Very Easy	9 (10.71%)	22 (26.19%)	
Presence of complications (minimal cervical laceration)	1 (2.38%)	3 (7.14%)	0.31

* Statistically significant: p-value < 0.05

Table 7. Patient acceptability.

	Laminaria (n = 42)	Evening Primrose Oil (n = 42)	P-value
Level of Pain	3 (1)	5 (0)	0.00*
Level of Discomfort	3 (2)	5 (1)	0.00*
Patient Complaints	2 (4.76%)	4 (9.52%)	0.01*
Bleeding	2 (4.76%)	4 (9.52%)	0.39
Cramping	22 (52.38%)	1 (2.38%)	0.00*
Diaphoresis	3 (7.14%)	-	0.24
Blurring of Vision	1 (2.38%)	-	0.5
Dizziness	1 (2.38%)	-	0.5
Vaginal discharge	-	1 (2.38%)	0.5
Nausea	1 (2.38%)	-	0.5
Foreign body sensation	-	1 (2.38%)	0.5

* Statistically significant: p-value < 0.05

patients randomized to the Evening Primrose Oil group did not experience pain. This difference was significant with a P-value of < 0.001

In terms of discomfort experienced during the period of cervical priming, majority of the patients in the Laminaria tent group were neither comfortable nor uncomfortable (Likert Scale of 3). Most of the patients in the Evening Primrose oil group were very comfortable during the period of cervical priming (Likert Scale of 5). The discomfort experienced by the patient in the Laminaria group was mainly due to cramping (52.38%). The discomfort experienced by the patients in both groups was statistically significant with a p-value of 0.01.

Discussion

Operative hysteroscopy is a common gynecologic procedure, which gives a panoramic view of the uterine cavity and direct biopsy of lesions, thus increasing diagnostic accuracy.¹⁷ The diameters of resectoscopes necessitate dilatation of the cervical canal to 10 or 11 mm prior to insertion of the instrument. The common complications encountered during hysteroscopy are mainly related to the difficulty of cervical dilatation, and include cervical tears, creation of false tracks and uterine perforation. This is why several agents have been suggested for cervical ripening, such as Laminaria tents and prostaglandin analogues.

Judging cervical width in millimeters preoperatively with dilators used in clinical practice is a normal method of assessing the effect of cervical ripening. Less commonly, preoperative ripening is assessed by measuring cumulative dilatation force using a cervical tonometer.¹⁷ Cervical resistance to dilatation or complications encountered during the procedure are also parameters that can indicate effectiveness of cervical ripening. A randomized, double-blind, placebo-controlled trial using misoprostol by Oppegaard and colleagues showed that a preoperative cervical dilatation of 5 mm was associated with easier cervical dilatation with Hegar's dilators, decreasing the risk of creating a false passage and frequency of complications.¹⁸

The purpose of this study is to compare the efficacy of Laminaria versus Evening Primrose Oil as cervical ripening agent prior to operative hysteroscopy and to compare the surgeon and the patients' acceptability of the cervical ripening agents.

The study population was homogenous for both groups and consisted mostly of premenopausal patients, with a mean age of 40, no history of any uterine surgery, and who presented with abnormal uterine bleeding and underwent hysteroscopic polypectomy.

The patients in the Laminaria group were mostly multiparous women who underwent vaginal deliveries and those in the Evening Primrose Oil group were mostly nulliparous women. It is expected therefore, that subjects under the Evening Primrose Oil group are predicted to undergo a more difficult and longer time to adequate cervical dilatation.

However, this study showed otherwise. Although the initial cervical dilatation was significantly greater for the Laminaria group (6.29 ± 1.66 cm) compared to the Evening Primrose Oil group (5.55 ± 1.73 cm), the amount of time necessary to be able to insert the resectoscope (Hegar's 10mm) after initial cervical dilatation was significantly shorter for the Evening Primrose Oil group (55 seconds) compared to the Laminaria group (123 seconds). This may be attributable to the production of prostaglandin E₂, which is known to cause cervical softening.¹³ Furthermore, based on the surgeons' acceptability, the subsequent cervical dilatation was significantly easier for the Evening Primrose Oil group (P-value 0.04), suggesting that the ease and speed of subsequent dilatation were more associated with degree of softening rather initial cervical dilatation.

Three patients (7.14%) in the Evening Primrose Oil group and one patient in the Laminaria group (2.38%) had minimal cervical laceration. Although this was higher than the reported 1 to 1.5% rate of complications for hysteroscopy, it was not statistically significant. No significant bleeding necessitating surgical repair occurred. All patients were asymptomatic on their post-operative follow-ups.

The pain on application of the cervical priming agent was greater for the Laminaria group and majority of the patients complained of abdominal cramping. This is mainly due to the difference in the route of administration of the two agents. Subjects in the Laminaria group had to undergo speculum insertion to facilitate intracervical placement of laminaria. On the other hand, Evening Primrose Oil capsules were inserted intravaginally using just a gloved hand, without the use of a speculum. Three patients experienced vasovagal symptoms (diaphoresis, blurring of vision, nausea) after Laminaria insertion (7.14%). The patients were maintained in recumbent position and monitored until symptoms resolved. The patients in the Evening Primrose oil were pain-free during application and were comfortable during the period of cervical priming.

Conclusion

This randomized controlled study comparing the efficacy of Laminaria tent and Evening Primrose Oil capsule showed that both agents were effective in dilating the cervix. However, the cervical softening properties of Evening Primrose Oil resulted in easier and faster cervical dilatation required for hysteroscopy. Furthermore, Evening Primrose Oil has better patient acceptability because it is more convenient and easier to use, and is less expensive, compared to Laminaria tents. Evening Primrose Oil capsules is an easy-to-use regimen that can be recommended for patients undergoing operative hysteroscopy, to facilitate easier cervical dilatation, and reduce complications associated with resectoscope entry.

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