

The effect of intrauterine instillation of E-Aminocaproic Acid during hysteroscopic operations in the management of intractable uterine hemorrhage: A Randomized Clinical Trial

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Abstract: The main objective of this study is to determine the effect of intrauterine instillation of ϵ -aminocaproic acid (EACA) during hysteroscopic operations in the management of uterine bleeding. Seventy participants have been considered for each group in a double blind, RCT in a teaching hospital in Tabriz University of Medical Sciences from Oct. 2010 to Dec. 2012. Patients with a history of abnormal uterine bleeding accompanied submucous myoma less than 4 cm in diameters, were included. Both groups received dextrose 5% as a distending media. Only in group 1, EACA acid added to injected media. Intrauterine bleeding during hysteroscopic surgery was determined by visual scale. Intraoperative bleeding, duration of surgery, the volume of injected media, and success in completion of operation were considered as primary outcomes and postoperative complication including gastrointestinal side effects, uterine bleeding, and duration of hospital stay are considered as secondary outcomes. Of 140 patients, 120 of them completed the study. Patients in group 1 had less intraoperative intrauterine bleeding compared to group 2 ($p = 0.02$). There was no statistically significant at the mean operation time ($P = 0.45$). Statistically significant differences were found between the two groups to create a very clear operative field. [RR = 2.82 95%CI (1.76 – 4.5) ($P < 0.001$)]. There was no significant intraoperative and postoperative complications in both groups ($p > 0.05$). The results showed that EACA is effective in reducing hysteroscopic intraoperative uterine bleeding. EACA makes a clear and un-blurred environment to achieve good surgical results. EACA is suggested for other uterine endoscopic surgeries.

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1. Introduction

Abnormal uterine bleeding (AUB) is a common health complaint of women and up to 14 percent of women experience irregular or excessively heavy menstrual bleeding (1). It can be caused by a wide variety of problems. In premenopausal women AUB could have anovulatory and ovulatory patterns. Ovulatory abnormal bleeding may emanate from definable pathologic entities in the endometrial cavity such as polyps and submucous leiomyomas (2). When clear structural causes are identified, the decision will be hysterectomy (1). However, this intervention is not an ideal option during a woman's reproductive years and submucous myomata no longer require hysterectomy because they can be satisfactorily managed conservatively by operative hysteroscopy (3). Operative hysteroscopy obtains a good environment to see and treat the uterine pathology (4). Although, hysteroscopy is an effective method for examining the uterine cavity but limited space inside the uterine cavity, inability to achieve a bright view and a satisfactory haemostasis are its potential limitations. Several options have been carried out to overcome the

problem, including instillation of viscid media. The major disadvantages of most types of distending media is absorption of the irrigation fluid and subsequent results such as life-threatening fluid overload and electrolyte disturbances if the duration of operation is long (5). To make a facilitation in performing hysteroscopic procedure, accurate fluid balancing, limiting the operation time and to create a bright view inside the uterine cavity, several strategies have been advocated. Some authors advocated preoperative use of danazol (6) and GnRH analogues (7,8), to reduce bleeding and the amount of fluid absorbed into the systemic circulation. The use of intrauterine prostaglandin F_{2α} has also been described to facilitate extrusion of type 2 myomas (9). These medications have resulted to less intraoperative complications but they could not control bleeding episode during surgery. Antifibrinolytic tranexamic acid (ϵ -Aminocaproic Acid, EACA), is one of the most effective medical therapy to treat heavy menstrual bleeding (10, 11). It is also used to treat or prevent excessive blood loss during surgery and in various other medical and surgical conditions such as elective cesarean section (12), postpartum haemorrhage

(13), and hemorrhagic cystitis (14). It has also been shown that tranexamic acid reduces blood transfusion in surgery and is effective and safe for the reduction of blood loss (15). In contrast, some investigators has not recommended it for routine use (16), and others showed an uncertain effects (17), or no additional benefit for intravenous infusion of tranexamic acid (18). So we decided to use the agent directly to the surgical site to obtain good surgical results. Satisfactory distension of the uterine cavity to obtain clear visualization of the space and sustain the view bright without bleeding during procedure is an important outcome. This study was planned to determine the effect of intrauterine instillation of EACA during hysteroscopic operations in the management of uterine bleeding during hysteroscopic surgeries, making a bright view during operation, reduce duration of surgery, intraoperative and postoperative complications during and after hysteroscopic resectoscopic surgery and successfully performing the procedure.

2. Methods

A double-blind RCT was conducted at Alzahra University-affiliated Teaching Hospital in Tabriz University of Medical Sciences from Oct. 2010 to Sept.2012. Seventy participants have been considered for each group. The initial sample size with the probability (power) of 0.08, was calculated to be 60 patient for each and the sample size was increased to 70 number for each group to enhance the validity of study. Participants were allocated to intervention (group 1) and control (group 2) groups according to the RandList (RandList version 1.2, DatIng GmbH, Tübingen, Deutschland; seed number: 1901365632). Each participant gave written consent to participate. Patients with the history of persistent moderate uterine bleeding accompanied submucous myoma less than 4 cm in diameters; type 0 or type 1, and patients' willing to participate were included. Patients with cardiopulmonary, hepatic, and renal diseases, hypertension, metabolic disorders including diabetes, and high serum lipids, who had genital infections, uterine septum or structural abnormality, history of cervical and uterine cancer and history of thrombophilia or who were taking anticoagulants, pregnant women, and patients who had severe bleeding were excluded. Preoperative assessment of the fibroid was based on transvaginal ultrasound. Preoperatively, official endometrial biopsy and pap smear were performed for all patients to rule out malignancy. Pre and post-operative evaluation was made according to the routine control of patients in addition to checking of hemoglobin and hematocrit, plasma sodium and potassium levels before and 6 hours after the surgery. In addition, Misoprostol 200µg administrated vaginally

on cervical priming 12 hours before the procedure. All procedures were performed under general anesthesia and all patients received saline normal during surgery. Mean time for cervical dilatation by Hegar series was omitted from total time. A monopolar resectoscope was used and dextrose 5%, was selected as a distending media. In cases (group 1), one gram of E-Aminocaproic Acid (TRANEXIP; Caspian Tamin Pharmaceutical Co. Iran), for every one liter of dextrose 5% and in controls (group 2), placebo i.e., dextrose 5% in the same form inside every one liter of the dextrose 5%, was used. The operative room temperature was used for instillation of the serums. Intrauterine bleeding during hysteroscopic surgery was determined by visual Likert scale between surgeon and circulate nurse in agreement, to estimate the amount of bleeding as no bleeding, mild, moderate and severe. The surgeon was not aware from the medication type which was used inside the serum. The need for transfusion, anesthetic complications, and decide to not continuing operation was made during surgery. Accurate measurement of the absorbed volume was made by a closed system. Intraoperative bleeding, the quality of view, duration of surgery, the volume of injected media, intraoperative complications including anesthetic side effects such as hypotension and bradycardia and success in completion of operation are considered as primary outcomes and documented. Levels of hematocrit, plasma sodium and potassium, 6 hours after surgery, length of hospital stay, postoperative complications including gastrointestinal side effects, headache, postoperative uterine bleeding, leg muscles cramp and duration of hospital stay are considered as secondary outcomes and were filled in data sheet. The study protocol was reviewed and approved by the Tabriz Research Affairs Review Board. Data were analyzed using both descriptive and analytic statistics. Values were given as the Means \pm SD and N and (%). The chi squared (χ^2) test, independent sample t- tests, and a repeated measurement ANOVA were performed on data. For all measurement parameters, differences were considered statistically significant at a p-value less than 0.05. All statistical analyses were performed using SPSS version 17.0 statistical software for Windows. The analyses was blind.

3. Results

One hundred and forty patients entered and 120 of them completed the study. In 20 patients (10 in each group) (28.4%), the procedure could not be proceeded because the uterine cavity did not distend at all. The patients' characteristics are shown in the table 1. There were no differences in demographic characteristics variable between the two groups.

Table 1. Demographic characteristics of participants

	Group 1 mean±SD	Group 2 mean±SD	P value
Age	39.6±7.8	40.9±9	0.39
Gravity	2.5±0.3	3.3±0.3	0.85
Parity	2.1±0.2	2.8±0.2	0.13

Instillation of EACA was resulted to complete removal of the myoma in 56.6% (N=34) (grade 0) and 33.3% (N=20) (grade 1) of myomas in group 1 compared to 26.6% (n=16) (grade 0) and 25% (n=15) of myomas in group 2, which the difference was significant ($p<0.001$). Two groups were compared in terms of blood loss. Overall women in group 1 had less intraoperative intrauterine bleeding compared to group 2 (table 2)($p < 0.022$).

Table 2. Amount of intraoperative intrauterine bleeding

	Severe N(%)	Moderate N(%)	Mild N(%)	No bleeding N(%)	P value*
Group 1	1 (1.7%)	9 (15%)	24(40%)	26 (43.3%)	0.022
Group 2	3 (5.1%)	21 (35.6%)	21 (35.6%)	14 (23.7%)	

*P value< 0.05 was considered significant

The mean operating time was 11±0.8 min and 10.8±0.9min for group 1 and 2, respectively which was not statistically significant ($p=0.45$). The results of χ^2 analysis showed that a very clear operative field was found in 43 (71.6%) of group 1 compared to 15 (25%) of group 2, which the difference was statistically significant [RR= 2.82 95%CI (1.76 – 4.5)]($P<0.001$). The results of instilled media volume, uterine size and myoma size are shown in table 3.

Table 3. The results of instilled media during hysteroscopy and uterus characteristics

	Group 1 mean±SD	Group 2 mean±SD	P value*
Media volum used	1.8±0.2	2.4±0.2	0.01
Endometrial thickness	10.0±0.7	11.1±0.9	0.51
Uterin size	88.3±2.5	94.7±3.5	0.10
Myoma size	23.7±4.1	34.6±6.7	0.30

*P value< 0.05 was considered significant

Independent samples T test showed that the difference between the means of the injected media volume between groups was significant and in group 2 was higher (1800±200 cc vs. 2400±200cc) ($P=0.01$). But there was no difference at the mean size of the fibroid (23.7±4.1 cm vs. 34.6±6.7 cm) ($P=0.30$) and

uterine size (88.3±2.5cm vs. 94.7±3.5 cm) ($P=0.51$), between groups. The mean of EACA was 2.8g (0.5-4). There was no difference at the location of myomas inside the uterine cavity. In most patients of both groups (58% vs 60%, respectively), the myoma was located at the fundal - anterior surface of the uterus. The results of χ^2 test showed that in 8.5% of group 1(n=5) and 8.3% of group 2 (n=5), the final results of pathology was endometrial polyp and two cases of endometrial hyperplasia was reported in group 2. There were no procedure-related complications in either group. There was also no significant postoperative complications in both groups. Only one case of nausea was reported in group 2. The levels of Hct before and 6 hours after the surgery was 37.2±6.4 and 34.5±5.3 in group 1 and 36.7±5.3 and 33.9±7.9 in group 2, respectively, which the difference between groups was not significant ($p=0.95$). In addition, there was no significant difference at the levels of Na⁺ and K⁺ between groups 6 hours after surgery ($p=0.45$). There was no difference between groups at discharge time and more than 50% of them discharged on operation day.

4. Discussion

The results of our study show that women who received EACA, met all two primary efficacy end points, first; a significantly greater reduction in intrauterine blood loss compared to women who received dextrose (table 2) ($P<0.001$) and higher bright view [RR= 2.82 95%CI (1.76 – 4.5)]; second, lower infusion volume ($p=0.01$), and a higher surgical satisfaction ($p<0.001$). The duration of surgery in EACA group was shorter than in dextrose group, however, it was not significant. There was also no significant adverse events including gastrointestinal adverse effects such as nausea and vomiting. There was no potential complications such as venous air and gas embolism, uterine rupture which need for cancelling of the procedure. In 10 patients in each group the uterine cavity had a restricted space, so the procedure abandoned.

In recent years hysteroscopy is performed extensively for both to view and treat the pathology within the uterine cavity. Although hysteroscopic resection of submucous myomas is considered a safe procedure, but absorption of the irrigation fluid and intraoperative bleeding may result in life-threatening complications (19). Accurate fluid balancing and limiting the operation time may prevent these complications (5). Selection of a distending media requires consideration of the advantages, disadvantages, and risks associated with various media as well as their compatibility with electrosurgical or laser energy (20). The most common perioperative complications associated with operative hysteroscopy

are hemorrhage (21). The walls of uterine cavity are so richly endowed with blood vessels that touching it with the sheath of the hysteroscope may invariably produces bleeding and for keeping the field clean, the clots need pushed apart or implement a strategy to reduce bleeding. To improve the procedure safety and minimize invasion some studies investigated preoperative administration of medications to overcome the intraoperative complications. The preoperative use of danazol (6) or GnRH analogues (8), may reduce operating time, bleeding and the amount of fluid absorbed into the systemic circulation and difficulty of the procedure. Endometrial thinning prior to hysteroscopic surgery in the early proliferative phase of the menstrual cycle improves both the operating conditions for the surgeon and short term post-operative outcome. Despite both agents produce satisfactory results, but the effect of these agents on longer term post-operative outcomes such as amenorrhoea and the need for further surgical intervention reduces with time (22). On the other hand, the value of pre-operative GnRH analogues to facilitate resection of myoma is uncertain and the reports show no benefit (23). In addition, intrauterine prostaglandin F_{2α} has been used to facilitate extrusion of type 2 myomas (9), but the effects of these medications during surgery is also unpredictable.

A variety of distending media have been used to achieve good visualization within the uterine cavity, but each one has some limitations and disadvantages such as vascular uptake, allergic reaction (5, 24, 25). Most complications could be avoided by closely monitoring fluid balance intraoperatively. In this study, we used dextrose 5%, because we were using a monopolar system. However, there was no hazard of this media relates to its vascular absorption and creation of an acute hyponatremic or hypo-osmolar state and the levels of Na⁺ and K⁺ were not changed after surgery. In addition, intraoperative intrauterine control of bleeding reduced both media over load and intrauterine bleeding, hence, gave opportunity to complete the procedure and prevented unpleasant outcomes. EACA which was used in this study, is a plasminogen activator inhibitors and approved by the U.S. Food and Drug Administration for the treatment of ovulatory bleeding. Plasminogen activators are a group of enzymes that cause fibrinolysis and the dissolution of clots. An increase in the levels of plasminogen activators has been found in the endometrium of women with heavy menstrual bleeding. Plasminogen activator inhibitors such as EACA and tranexamic acid have therefore been promoted as a treatment for heavy menstrual bleeding in oral form or parenterally (26, 27). It is also used during surgery to prevent clot breakdown (fibrinolysis) in order to reduce surgical blood loss (15, 28-30). In contrast, according to

Cochrane Database System Review, tranexamic acid has not been recommended for routine use (16). Raviraj and colleagues in their study showed that tranexamic acid reduces blood transfusion in surgical patients while its effects on thromboembolic events and mortality are uncertain (17). Caglar and co-workers in their study to define the effect of tranexamic acid use on perioperative and postoperative bleeding and blood transfusion requirements in women undergoing myomectomy, did not found any additional benefit for intravenous infusion of tranexamic acid (18). Although there has been a reluctance to prescribe tranexamic acid due to possible side effects of the drugs such as an increased risk of thrombotic disease (deep venous thrombosis), long term studies in Sweden, however, have shown that the rate of incidence of thrombosis in women treated with tranexamic acid is comparable with the spontaneous frequency of thrombosis in women (10, 11, 26). Therefore, EACA can be used to obtain good results without side effects. EACA is administered intraoperatively and affect directly on bleeding from the uterine wall and myoma bed, reduce operating time and systemic absorption of distension media, facilitate complete removal of myoma and more importantly, they make a bright view to follow the procedure completely. The limitation of this study was the small sample size, and different myoma size. These promising findings need to be confirmed by well-designed and adequately powered prospective study with large sample size using patient-related outcomes and by carefully examine the safety and efficacy of these agents.

5. Conclusion

This study confirms that hysteroscopic resectoscopy with instillation of EACA is a safe, and rapid surgical procedure with no complications, which is peculiar to a good patients' outcome. Addition of EACA to the fluid medium resulted to create a very clear operative field, bright and un-blurred environment to achieve good surgical results, which allowed the operator to see operative site continuously without interruption of the procedure. EACA was effective in reducing intraoperative and postoperative bleeding, operative duration, intraoperative and postoperative complications. This approach could be used in other uterine endoscopic surgeries and with other distending media or bipolar instruments.

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Conflict of interest:

Authors declare that they have no conflict of interest.

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