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Effect of oxytocin infusion on reducing the blood loss during abdominal myomectomy: a double-blind randomised controlled trial

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Objective To assess the effectiveness and safety of oxytocin to reduce blood loss during abdominal myomectomy.

Design Double-blind randomised controlled trial.

Setting Obstetrics and Gynecologic University Medical Centre.

Population Eighty healthy women candidates for abdominal myomectomy.

Methods Women were randomly assigned to two groups. In the study group (n = 40) oxytocin 30 IU in 500 ml normal saline; and in the placebo group (n = 40) pure normal saline was administered during myomectomy. The main outcome measures were peri-operative blood loss and rates of blood transfusion.

Main outcome measure Estimated intra-operative blood loss.

Results Estimated intra-operative blood loss in the study group (189.5 ± 16.72 ml) was significantly lower than the placebo group (692.25 ± 89.93 ml) (95% CI 672.54–711.96; $P < 0.0001$).The need for blood transfusion was significantly lower in the study group. Blood transfusions were required for three (7.5%) women in the study group and 10 (25%) women in the placebo group (95% CI 15.5–34.5; $P < 0.001$).

Conclusions Intra-operative oxytocin infusion appears to be safe and effective in decreasing blood loss during abdominal myomectomy.

Keywords Abdominal myomectomy, blood transfusion, intra-operative blood loss, oxytocin.

Tweetable abstract Intra-operative oxytocin is effective in decreasing blood loss during abdominal myomectomy

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Introduction

Uterine leiomyomas (fibroids) are the most common benign tumours among women.[1] Fibroids are found in approximately 20% of women over 35 years of age.[2] In 20–50% of patients, fibroids may cause problems such as heavy menstrual bleeding, anaemia, pelvic pain and pressure, and symptoms from extrinsic compression of the colorectal and urinary tract.[1–3] Surgery is indicated for symptomatic uterine leiomyomas; hysterectomy for women who have completed childbearing (women > 40 years old), and myomectomy for women <40 years old who wish to preserve uterine and fertility.[4]

Trial Registration: Iranian Clinical Trial Registration number: IRCT201211217013N3 (http://en.search.irct.ir/view/11549).

Myomectomy can be accomplished by laparotomy, laparoscopy, or hysteroscopy (transvaginal)[1,5–8] approaches. This surgical procedure may be associated with substantial morbidity, in particular major blood loss,[9] especially in abdominal myomectomy. Blood transfusion can be required in up to 20% of the women during abdominal myomectomy.[10] A number of interventions have been introduced to reduce bleeding rate during myomectomy, such as use of tourniquets, uterine artery dissection, vaginal misoprostol, intra-myometrial infiltration of bupivacaine plus epinephrine, injection of vasopressin into the uterus, preoperative administration of gonadotropin-releasing hormone (GnRH) agonist, and peri-operative injection of ascorbic acid. However, these strategies may be associated with some complications, and some of these are ineffective or expensive or required extra steps before the actual procedure.[1,8,11–16]

Oxytocin is a hormone secreted mainly from the pituitary gland. Its main function is uterine contraction during labour and delivery. Oxytocin is the agent of choice in the prevention of postpartum uterine atony and bleeding,[16–18] but should be used cautiously because an intravenous bolus of 10 IU oxytocin could be detrimental to women with heart disease or to women who are hypovolemic.[19] Oxytocin receptors exist in the non-pregnant uterus, although the concentration of the receptors is much lower than in its pregnancy. It is for this reason that the clinical use of oxytocin outside of pregnancy is limited.[20–22]

Myomectomy is an operation where significant haemorrhage can occur. In light of the effectiveness of oxytocin on the postpartum uterus, there is interest in the use of oxytocin to reduce uterine perfusion and therefore bleeding during myomectomy. Shokier et al.[20] reported that oxytocin infusion reduces the observed reduction in haematocrit after hysteroscopic myomectomy. Wang et al.[16,21] discovered the ability of oxytocin to reduce the haemorrhage and subsequent blood transfusion requirement during laparoscopic myomectomy and laparoscopic vaginal hysterectomy. The one published randomised double-blind study did not show any benefit of using oxytocin in preventing bleeding during abdominal and vaginal myomectomy.[22] In view of the lack of data, we designed a trial to evaluate the efficacy of peri-operative administration of oxytocin on reducing bleeding during abdominal myomectomy.

Methods

Trial design

This was a single-centre, controlled, double-blinded trial with randomisation in two parallel groups, with intervention and placebo allocation ratio 1:1. Approval from the hospital Ethics Committee (N#915, Date; 18 November 2011) and Research deputy of Tabriz University of Medical Sciences (N#91126, Date; 7 April 2013). The study was conducted at Al-Zahra university Hospital (Tabriz, Iran) from 30 November 2011 to 20 Jun 2015 on patients who were candidates for elective abdominal myomectomy. All patients enrolled to this study signed a written informed form. Eighty patients were studied. This study was conducted from 10 November 2012 to 15 Jun 2015 in Al-Zahra teaching Hospital, Tabriz, Iran. The trial was registered at Iranian Clinical Trial Registration with approved number of IRCT 201211217013N3. (https://www.irct.ir/).

Women with ASA physical status class I–II, aged >30 years, and intramural fibroids (diagnosed by ultrasound imaging) who were candidates for elective abdominal myomectomy were enrolled to this study. Patients with cardiovascular or respiratory disease, preoperative haemoglobin concentration <10 g/dl, body weight >85 kg, were planned for hysteroscopic or laparoscopic myomectomy, and patients with sub-mucosal fibroids were excluded from the study. None of the patients had received preoperative GnRH analogues**.** Patients were allocated into study and placebo groups, according to a two blocked randomisation list that was prepared using online software at a 1:1 ratio. The list was coded (A or B) that was preprinted in sealed-envelope packets. Except for one of authors (SA), all were blinded to the treatment solution for every patient during the study.

After induction of general anaesthesia and immediately prior to the operation, an infusion of 30 IU oxytocin in 500 ml normal saline at a rate of 120 ml/h was started in study group patients during myomectomy. In placebo group patients, a pure normal saline infusion was used at the same volume and rate. In all operations, the abdomen was exposed through a Pfannensteil incision. Two fixed anaesthetists and one gynaecological surgeon, who were all blinded to the treatment solution, were responsible for anaesthetic and surgical management of the patients during the study. The anaesthetists visited the women every hour during the first 6 hours, and then at 12, 24 and 48 hours post-operatively and every additional 24 hours thereafter until discharge.

The primary clinical outcome was intraoperative blood loss (ml), which was calculated and recorded by a trained medical student. The use of blood transfusion was also recorded. According to common guidelines, the decision for blood transfusion was upon the estimated amount of bleeding, clinical signs including arterial blood pressure and heart rate (HR), and haemoglobin concentration <10 g/dl. Blood loss was estimated by calculating the sum of canisters containing irrigation fluids and suctioned blood minus used irrigation solution plus the amount of absorbed blood in used sponges (estimated by weighing dry sponges before the operation and then wet sponges at the end of surgery). Post-operatively, the indication for blood transfusion was clinical findings plus haemoglobin concentration <10 g/dl.

Secondary clinical outcomes included: the need for intra-operative and post-operative transfusion (numbers/percent of patient in each group), preoperative and post-operative haemoglobin and haematocrit values (measures at 6 hours before and 24 hours after surgery); peri-operative blood pressure and HR, time of ambulation (interval the operation ended up patient's walking with assistance), and period of hospitalisation (post-operative hospital stay). In addition to demographic characteristics, as well as the size and number of preoperative intramural fibroids (established by sonography), uterus size in pelvic examination, and operation and anaesthesia time were recorded.

Statistical analyses

The sample size was calculated on the basis of results of an earlier study by Wang et al.[16] For an inter-group mean (SD) difference of 200 ml in blood loss, it was calculated that approximately 40 patients were required in each group, with a power of 0.9 and level of significance of 0.05. Statistical analysis was performed using SPSS software version 15.0 (SPSS, Chicago, IL, USA). Independent samples Student's *t*-test was used for comparing normal distribution numerical data between two groups, and Chi square or Fisher's exact tests for categorical data. The distribution normality was tested using Kolmogorov–Smirnov test. Changes in Hb, Hct were compared between two groups using paired samples Student's *t*-test. Repeated measures of analysis of variance (ANOVA) test was used for analysing the mean arterial pressure (MAP) and HR changes during surgery within every group. *P*-values <0.05 were considered statistically significant. Parametric data are presented as mean (SD), and nonparametric data as frequency (%).

Table 1. Patient's characteristics and preoperative variables in two groups

	Study group (n = 40)	Placebo group (n = 40)	*P*
Age (years)	38.08 ± 0.74	36.25 ± 0.74	0.62
Weight (kg)	67.35 ± 1.59	68.78 ± 1.56	0.99
Height (cm)	160.25 ± 0.75	160.65 ± 0.68	0.26
Gravidity (number)	0–4	0–3	0.85
Uterine size (week)	14.8 ± 0.25	15.05 ± 0.62	0.74
Largest fibroid	14.8 ± 0.25	15.05 ± 0.62	
Length	70.45 ± 4.15	72.80 ± 5.52	0.32
Width	66.33 ± 3.36	68.95 ± 5.61	0.45

Data are presented as mean ± SD or range, based on Student's *t*-test.

Results

Figure 1 shows the flowchart diagram of study. The groups were similar with respect to demographic data and preoperative clinical data (Table 1). Intra- and post-operative data were presented in Table 2. Intra-operative approximate blood loss in the study group (189.5 ± 16.72 ml) was significantly lower than the placebo group (692.25 ± 89.93 ml) (95% CI 672.54–711.96; $P < 0.0001$). The need for blood transfusion was significantly lower in the study group. Blood transfusions were required for three (7.5%) patients in the study group and 10 (25%) patients in the placebo group (95% CI 15.5–34.5%; $P < 0.001$).

Preoperative haemoglobin and haematocrit values were similar between groups. Reduction in these variables at 24 hours after surgery was more in the placebo group than the study group ($P < 0.0001$ for both parameters). Peri-operative haemodynamic variables did not show any statistically significant differences between the two groups, but decreasing the MAP and changes in HR from base values during the infusion of the study solutions were more apparent in the study group than the placebo group. However, these changes were within the normal range. Only the HR 30 minutes after drug administration was significantly different between the two groups, but both observed HRs

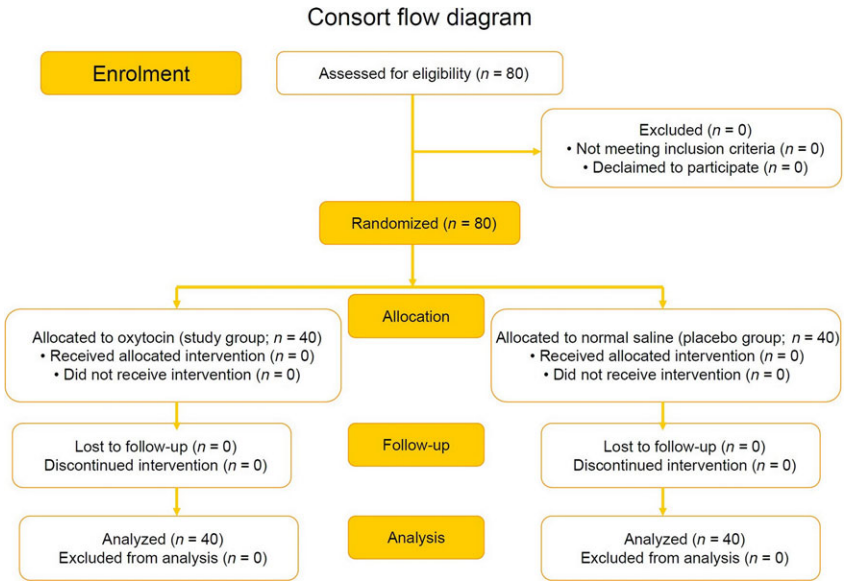

Figure 1. Flow chart of patients enrolled to the study.

Table 2. Peri-operative variables in study two groups

	Study group (n = 40)	Placebo group (n = 40)	P
Total intra-operative iv fluid (ml)	2643.75 ± 60.92	3278.75 ± 125.51	0.003
95% CI (range)	13.35 (2630.4–2657.1)	27.5 (32.51–3306.25)	
Minimum/maximum	2000/3500	2000/5500	
Urinary output (ml)	427.5 ± 31.12	595.0 ± 61.9	0.005
95% CI (range)	6.82 (420.68–434.32)	13.56 (581.44–608.56)	
Minimum/maximum	120/1000	200/2000	
Intra-operative calculated blood loss (ml)	189.5 ± 16.72	692.25 ± 89.93	<0.0001
95% CI (range)	3.66 (185.84–193.16)	19.71 (672.54–711.96)	
Minimum/maximum	30/400	150/3000	
Patients who needed to blood transfusion (%)	3 (7.5)	10 (25)	0.01
95% CI (range)	3.74 (−0.74 to 6.74%)	9.49 (15.51–34.49%)	
Number of removed fibroid	2.18 ± 0.26	2.53 ± 0.32	0.15
95% CI (range)	0.06 (2.12–2.24)	0.07 (2.46–2.60)	
Minimum/maximum	1/9	1/8	
Preoperative Hb (g/dl)	12.87 ± 0.24	12.66 ± 0.19	0.15
95% CI (range)	0.05 (12.82–12.92)	0.04 (12.62–1270)	
Minimum/maximum	9.1/15.0	9.5/15.4	
Postoperative Hb (g/dl)	11.47 ± 0.22	10.47 ± 0.17	0.24
95% CI (range)	0.05 (11.42–11.52)	0.04 (10.43–10.51)	
Minimum/maximum	8.1/13.8	7.8/12.1	
Preoperative Hct (%)	38.99 ± 0.7	38.76 ± 0.56	0.29
95% CI (range)	0.15 (38.84–39.14)	0.12 (38.64–38.88)	
Minimum/maximum	28.0/48.3	29.0/44.0	
Postoperative Hct (%)	35.1 ± 0.66	31.98 ± 0.5	0.32
95% CI (range)	0.14 (34.96–35.24)	0.11 (31.87–32.09)	
Minimum/maximum	27.0/45.0	25.0/37.5	
Decrease Hb from base value (g/dl)	1.40 ± 0.88	2.19 ± 1.18	<0.001
95% CI (range)	0.19 (1.21–1.59)	0.26 (1.93–2.45)	
Minimum/maximum	0.1/3.3	0.2/5.0	
Decrease Hct from base value (%)	3.89 ± 3.02	6.70 ± 3.50	<0.001
95% CI (range)	0.66 (3.23–4.55)	0.77 (5.93–7.47)	
Minimum/maximum	1.0/10.3	0.6/13.2	
Duration of operation (min)	97.55 ± 2/62	110.58 ± 3.79	0.01
95% CI (range)	0.57 (96.98–98.12)	0.83 (109.75–111.41)	
Minimum/maximum	42.0/133.0	65.0/170.0	
Duration of anaesthesia (min)	114.45 ± 2.62	130.35 ± 3.91	0.02
95% CI (range)	0.57 (113.88–115.02)	0.86 (129.49–131.21)	
Minimum/maximum	63.0/150.0	86.0/170.0	
Time of ambulation (h)	6.98 ± 0.38	9.59 ± 0.58	0.03
95% CI (range)	0.08 (6.9–7.06)	0.13 (9.46–9.72)	
Minimum/maximum	4.3/12.0	3.3/20.3	
Hospitalisation period (day)	2.05 ± 0.05	2.3 ± 0.08	<0.001
95% CI (range)	0.01 (2.04–2.06)	0.02 (2.28–2.32)	
Minimum/maximum	1.0/3.0	1.0/3.0	

Data are presented as mean ± SD, and number (%), based on X^2 analysis and Fishers exact test.

were within normal parameters (Figure 2). There were statistically significant differences between the two groups with regard to duration of surgery ($P = 0.01$) and anaesthesia ($P = 0.02$), and time of ambulation ($P = 0.03$) or hospitalisation period ($P < 0.0001$). No major side-effects were observed in either group.

Discussion

Main findings

This study showed that infusion of 30 IU oxytocin during abdominal myomectomy resulted in reduction in intra-operative blood loss and reduced need for blood transfusion

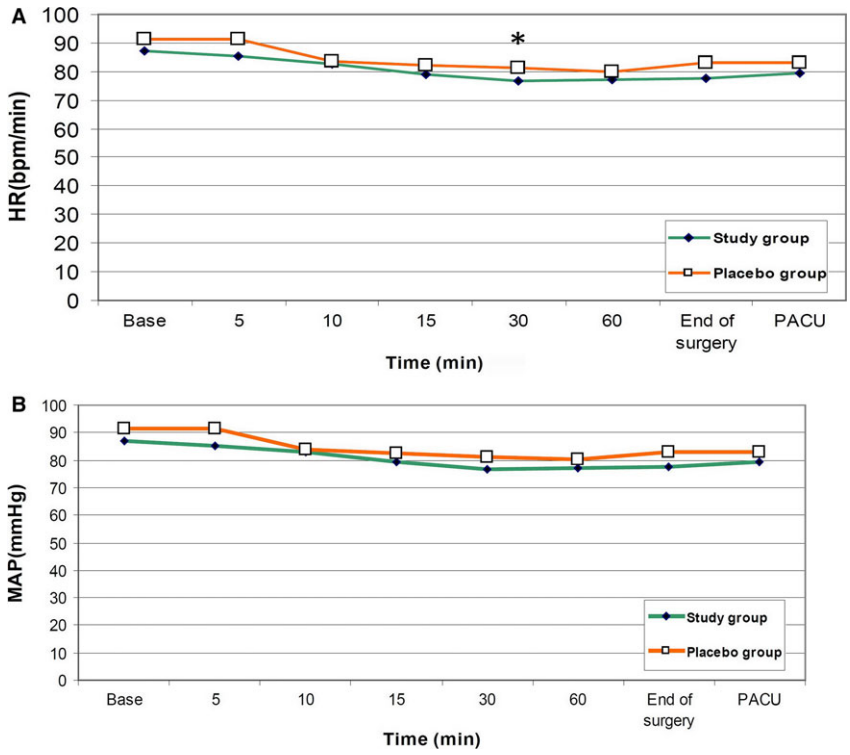

Figure 2. (A) Heart rate (HR) and (B) mean arterial pressure (MAP) changes at baseline and after starting treatment drug in study (oxytocin) and placebo groups, based on repeated ANOVA test. *$P < 0.05$.

when compared with placebo. Oxytocin affects oxytocin receptors in the myometrium and fibroid tissue, which stimulates synthesis and release of contractile prostaglandins. Increased uterine contractility directly affects uterine vascular structures, decreasing blood supply to the arteries and fibroids. Decreased blood volume in the uterus and constricted uterine vasculature due to uterine contraction and vaso-constrictive effect of oxytocin results in reducing intra-operative blood loss. Blood transfusion is reported to be required in up to 20% of women undergoing abdominal myomectomy.[4,10,11,14] In the present study, 25% of patients in the placebo group needed blood transfusion compared with only 7.5% in the group receiving an oxytocin infusion.

No side-effects of oxytocin usage were noted. Major side-effects of oxytocin include hypotension, tachy-arrhythmias or hyponatremia.[19,20] The reason for the lack of such complications in our study probably reflects the relatively low dose of oxytocin related.[23,24] In this study, mobilisation was on average nearly 3 hours earlier in the oxytocin groups, which may have been an important factor in preventing thromboembolic complications.

Strengths and limitations

The study was a blinded randomised controlled design minimising the risks of selection and observer bias. Limitations of this study include its small size and a lack of longer-term follow-up of women after discharge from hospital. By using a single, trained and blinded observer to estimate intraoperative blood loss, we hoped to standardise the calculation and improve its accuracy, although a degree of error is inevitable although this should apply non-differentially. It was not possible to calculate the amount of irrigation fluid collected in the sponges. Whilst we recorded the number of fibroids removed at surgery, we did not weight the overall removed fibroid mass which, if different between groups, could introduce bias. Because there is little evidence for the safety of higher doses of oxytocin, we did not use high doses of it.

Interpretation

The present study corresponds with the studies by Wang et al.[16,21] In the first study,[21] they observed that the infusion of oxytocin during laparoscopic-assisted vaginal hysterectomy for large uterus helped to decrease intra-operative blood loss, and the need for blood transfusion, and showed a decrease in post-operative haemoglobin concentration and haematocrit (Hb/Hct). In the next study,[16] they infused oxytocin during laparoscopic myomectomy, and concluded that oxytocin infusion may decrease operative blood loss and blood transfusion. Considering increased

blood loss in abdominal myomectomy, the finding may not be extended to these patients. Shokeir et al.[20] evaluated the effects of oxytocin drip on operative blood loss and irrigation fluid (glycine) deficit during hysteroscopic endometrial resection. They concluded that oxytocin infusion during the procedure induced uterine contraction, thus reducing uterine perfusion, as well as the intra-operative glycine deficit. The same mechanism that can reduce intra-operative bleeding is by oxytocin. They also suggested there is a trend toward a decrease in operative blood loss, and a need for further randomised trials to confirm their findings.

The findings of our study are transferable to similar women undergoing abdominal myomectomy. We did not evaluate laparoscopic myomectomy such is becoming increasingly adopted. Laparoscopic myomectomy requires appropriate laparoscopic dissection and suturing skills, can be time- consuming, and the technique is limited to the size, number and localisation of fibroids. Thus, abdominal myomectomy still plays a substantial role in the treatment of symptomatic fibroids in young females. The results of our study contrast with the findings of Agostiny et al.[22] The possible explanation of the opposite result may be the use of higher doses of oxytocin (30 IU oxytocin as a slow injection) administered in our study.

Conclusion

The infusion of oxytocin intra-operatively may be a safe and reliable method to help decrease blood loss during abdominal myomectomy. Further trials with different doses and protocols are necessary to confirm these findings.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

SA and SF contributed to the concept and planned the study frame, and they were responsible for the preoperative visit and premedication. EB prepared the two blocked randomisation lists of the patients with online software. According to the randomisation list, SA prepared the study solution and, except SA, all other authors were blinded to the treatment solution until the end of study. AA was responsible for blind data collection and recording. EB with the consult of a social medicine specialist had the responsibility of data analysing, continuous study progress monitoring and managing study methodology. SF and HP (anaesthesiologists) and PMG (gynecological surgeon) were responsible for anaesthetic and surgical management of the patients during the study, respectively. SF, SA and EB prepared the manuscript for publication. All authors reviewed and approved the final version of the manuscript.

Details of ethics approval

The study was approved by the Research Ethical Board of Tabriz University of Medical Sciences (N#91126, Approval Date; 7 April 2013).

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