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GENERAL GYNECOLOGY

Oxytocin infusion reduces bleeding during abdominal myomectomies: a randomized controlled trial

Berna Aslan Çetin[1] · Begüm Aydoğan Mathyk[2] · Nadiye Köroğlu[1] · Ali Soydar[1] · Gökhan Demirayak[3] · Tayfur Çift[4]

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Abstract

Purpose To evaluate the effectiveness of oxytocin infusion to reduce intraoperative bleeding during abdominal myomectomies.

Methods This randomized, parallel group, blinded study was conducted between October 2017 and May 2018. Patients undergoing abdominal myomectomies were randomized 1:1 either to the oxytocin group or to the control group (saline). In the oxytocin group, 10 IU oxytocin in 500 ml of saline at a rate of 120 ml/h was given during the course of the operation. The primary outcome of this study was to measure intraoperative blood loss between the study groups. Correlation and multiple regression analysis were performed to illustrate factors associated with intraoperative blood loss during the myomectomy.

Results The mean intraoperative blood loss during the surgery was 489.20 ± 239.72 ml in the oxytocin group and was 641.40 ± 288.21 ml in the control group. The hemoglobin decline was more evident in the control group than in the oxytocin group. Positive correlations were also observed between the intraoperative blood loss and number of fibroids removed during the surgery, largest fibroid removed and weight of fibroids removed. The use of oxytocin infusion during the myomectomy resulted in a reduction of bleeding in the regression model.

Conclusion Intravenous oxytocin infusion is a safe and practical method to reduce intraoperative blood loss during the abdominal myomectomy.

Keywords Myomectomy · Oxytocin · Intraoperative blood loss · Uterine fibroids

Introduction

Uterine fibroids are the most common benign tumors within the female reproductive system [1]. Although fibroids are mostly asymptomatic, 20–50% of women had menorrhagia, pelvic pain and urinary complaints [1]. Severity of the symptoms depend on size, number and the location of the fibroid [1]. Myomectomy is a surgery designed for women who have symptomatic fibroids and wish to preserve their fertility [2, 3]. Women with myomatous uteri have an increased number of blood supply which may cause excessive bleeding during myomectomy. The excessive bleeding may result in transfusions and prolonged hospital stays [4]. A variety of methods are used to reduce bleeding during myomectomy including preoperative administration of gonadotropin-releasing hormone (GnRH) agonists, uterine artery tourniquet, vaginal misoprostol, intravenous tranexamic acid, intramyometrial injections of bupivacaine plus epinephrine and vasopressin, chemical dissection with Mesna (sodium-2-mercaptoethanesulfonate) and perioperative injection of ascorbic acid [4–12]. Like GnRH, oxytocin is another hormone that exerts its effect on the uterus. It is secreted from the posterior pituitary and contracts the uterus during labor and delivery. Because of this contractile feature, synthetic oxytocin analogues are used in the treatment of postpartum uterine atony and bleeding [13, 14]. Oxytocin receptors are also present in the nonpregnant uterus [15]. In the last few years, synthetic oxytocin analogues have been introduced in

✉ Berna Aslan Çetin
bernaaslan14@hotmail.com

[1] Department of Obstetrics and Gynecology, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Altınşehir, 34303 Halkalı, Istanbul, Turkey

[2] Mother Infant Research Institute at Tufts Medical Center, Boston, MA, USA

[3] Obstetrics and Gynecology Department, İstanbul Sadi Konuk Training and Research Hospital, Istanbul, Turkey

[4] Obstetrics and Gynecology Department, Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Turkey

gynecologic procedures including hysterectomies, myomectomies and endometrial resections to decrease bleeding [16–18]. Limited data are available on the dosage amounts of oxytocin used during myomectomies. Thus, our aim is to investigate the affect of oxytocin infusion on intraoperative blood loss during abdominal myomectomies.

Materials and methods

This randomized, parallel group, double-blinded study was conducted at Kanuni Sultan Suleyman Research and Training Hospital, Turkey between October 2017 and May 2018. The study was approved by the Kanuni Sultan Suleyman Research and Training Hospital Ethics Committee and registered to ClinicalTrials.gov (NCT03308643). Informed consent was obtained from all participants before enrollment into the study.

Women 18–50 years old who were candidates for an abdominal myomectomy with symptomatic intramural fibroids (menorrhagia, pelvic pain, and/or urinary complaints) and intramural fibroids > 5 cm were included in this study. Patients with preoperative anemia, history of previous myomectomy, history of hormone therapy before the surgery, pregnant and postmenopausal women were excluded from the study.

Patients undergoing myomectomies were randomized by an online software and were sequenced 1:1 either to the oxytocin group or to the control group (saline). Sealed envelopes were opened sequentially by the anesthesiologist in the OR prior to the surgery. In the oxytocin group, intravenous oxytocin infusion started just before the surgery, after the induction of general anesthesia. 10 IU oxytocin (Synpitan®, Deva, Istanbul, Turkey) in 500 ml of saline at a rate of 120 ml/h was given during the course of the operation. In the control group, patients received 500 ml of saline infusion at the same rate. All cases had an abdominal myomectomy procedure starting with a Pfannenstiel skin incision, 2 cm above the pubic symphysis. Neither uterine artery tourniquet or intramyometrial injection of any hemostatic agents were used. Participants and the surgeon (B.A.C) were blinded to the assignment of the solution used.

In addition to demographic characteristics of the study population, size of the uterus during pelvic examination, number of fibroids removed, weight of fibroids removed, size of the largest fibroid removed, operation time and duration of hospital stay were also recorded.

The primary outcome of this study was to measure intraoperative blood loss (IBL) between the oxytocin and control groups. Blood loss was calculated by the addition of the blood volume in a canister to the total weight of pads [pad count × (wet pad weight − dry pad weight)]. The secondary outcomes included the number of blood transfusions and the comparison of the preoperative/postoperative hemoglobin and hematocrit values.

Sample size was calculated using G*power software. The sample size was 84, using the formula of 0.8 effect size, alpha error of 5%, and allocation ratio of 1. A final sample size of 100 was achieved by adding a 20% dropout rate to the prior calculation.

Data analysis was performed using the SPSS version 21 for Windows (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 7.0d (GraphPad Software, California, USA). The D'Agostino & Pearson normality test was used for the distribution of variables. Numerical variables were compared using the independent samples *t* test or the Mann–Whitney *U* test. Spearman correlation coefficient was used to explore the relationship between the continuous variables and the intraoperative blood loss. A multiple regression analysis was carried out to examine the contribution of factors associated with intraoperative blood loss during myomectomies.

The data are expressed using mean values with standard deviations. A $p < 0.05$ value was considered statistically significant.

Results

100 participants were included into final analysis (Fig. 1). The demographic data and preoperative parameters of the study groups were similar (Table 1). The mean intraoperative blood loss (IBL) during the surgery was 489.20 ± 239.72 ml in the oxytocin group, whereas, IBL was 641.40 ± 288.21 ml in the control group ($p = 0.005$, Table 2). The hemoglobin decline was more evident in the control group than in the oxytocin group (1.49 ± 1.01 g/dl vs 1.98 ± 1.24 g/dl, $p = 0.03$) (Table 1). Two patients had blood transfusions during the postoperative period in the oxytocin group, while eight patients had transfusions in the control group (4% vs 16%, $p = 0.04$) (Table 1). The operation time was similar between the groups (Table 1). There was no significant difference between the two groups in terms of weight of fibroids removed, number of fibroids removed and the largest fibroid removed (Table 1). We did not observe any complications in both groups.

In the correlation analysis, we found a significant direct relationship between the intraoperative blood loss and operation time as well as the preoperative size of the uterus during the pelvic examination (Table 2). Additionally, positive correlations were also observed between the intraoperative blood loss and number of fibroids removed during the surgery, largest fibroid removed and weight of fibroids removed (Table 2).

We also conducted a multiple linear regression analysis to understand the impact of the aforementioned independent variables on intraoperative blood loss (Table 3). The

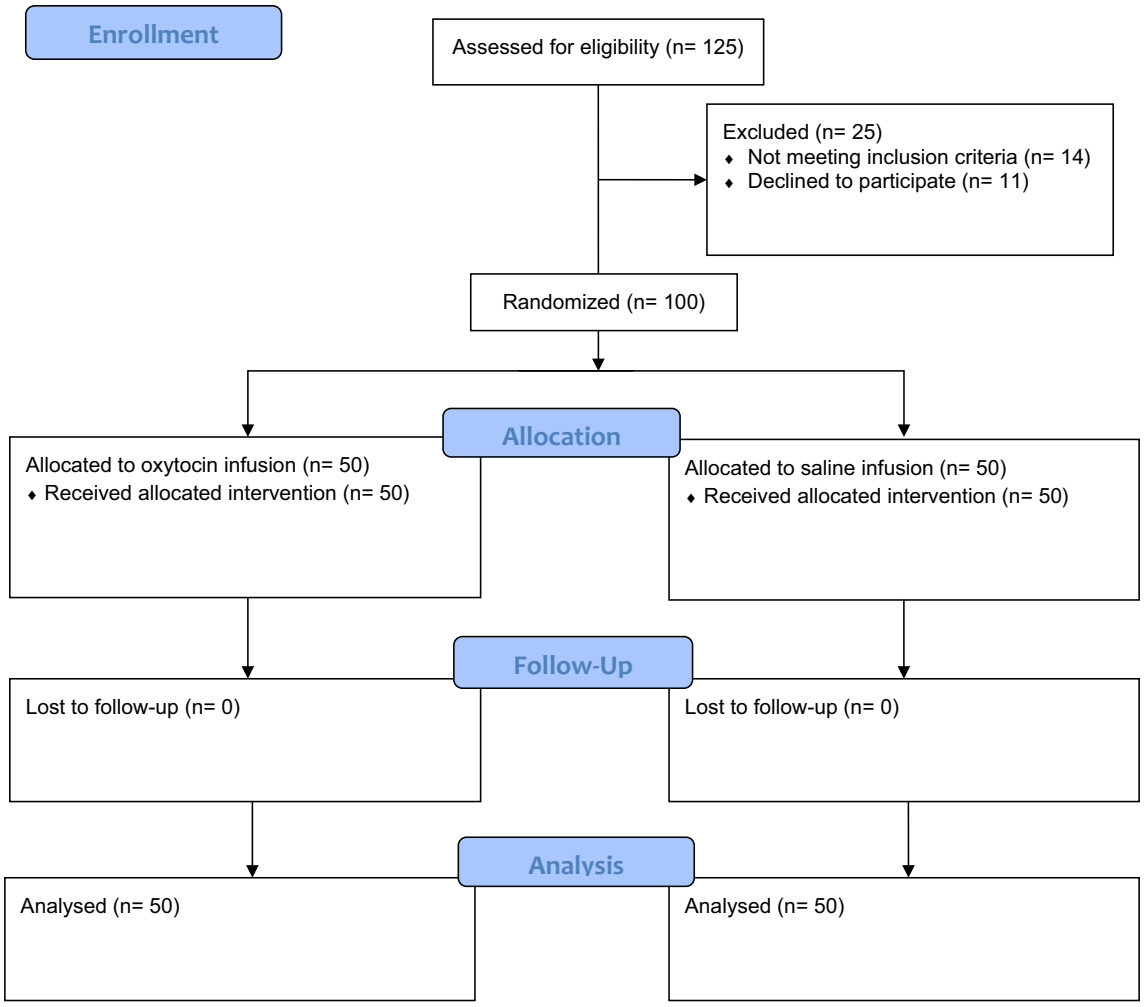

Fig. 1 Flow diagram

analysis included oxytocin use, operation time and features of fibroids. These features included the uterine size during the pelvic examination, number and total weight of fibroids removed as well as the largest fibroid removed during the surgery. The use of oxytocin infusion during the myomectomy resulted in a reduction of bleeding in the regression model (Table 3). For every one unit increase in the oxytocin use, the IBL decreased by (−0.23). The total weight of fibroids removed during the surgery and operation time was also a positive predictor of IBL (Table 3). Finally, we calculated an 81% post hoc power, based on intraoperative blood loss between the two groups.

Discussion

This study showed that oxytocin infusions (10 IU in 500 ml) during abdominal myomectomies reduces both intraoperative blood loss and the need for blood transfusions. Our study also revealed that intraoperative blood loss during the myomectomy directly correlated with fibroid properties such as numbers and weights of the removed fibroids. In the regression analysis, oxytocin use was the most important parameter reducing blood loss during surgery.

Uterine fibroids have rich a blood supply [19] which may result in intensive bleeding during the myomectomy procedure. Various management options have been used to reduce hemorrhaging during the myomectomy [4]. Some common treatments to prevent blood loss are the embolization of uterine arteries, use of tourniquets and injections of hemostatic agents.

Preoperative uterine embolization decreases blood loss during a myomectomy, however, this option is limited by the accessibility of equipment and by having trained physicians to complete the procedure [20]. Use of tourniquets and clamping of the uterine arteries were also effective in decreasing blood loss during the operation, but these techniques require extra steps during the procedure [21].

Table 1 Comparison of the demographic data, pre-and postoperative variables of the study groups

	Oxytocin ($n=50$)	Control ($n=50$)	p
Age (years)	36.66 ± 5.47	36.72 ± 4.69	0.953
Gravidity	2.34 ± 1.66	1.94 ± 1.50	0.210
Parity	1.72 ± 1.27	1.66 ± 1.30	0.817
BMI (kg/m^2)	25.54 ± 3.53	25.74 ± 2.99	0.761
Smokers *n* (%)	13 (26)	15 (30)	0.656
Previous abdominal surgery *n* (%)	14 (28)	18 (36)	0.391
Size of the uterus during the pelvic examination (weeks)	14.20 ± 3.43	15.16 ± 4.12	0.209
Preoperative hgb (g/dl)	11.5 ± 1.59	11.87 ± 1.51	0.233
Postoperative hgb (g/dl)	9.99 ± 1.55	9.86 ± 1.46	0.731
Preoperative hct (%)	35.85 ± 4.69	36.5 ± 3.92	0.437
Postoperative hct (%)	31.19 ± 3.96	30.89 ± 3.98	0.716
Hgb decline (g/dl)	1.49 ± 1.01	1.98 ± 1.24	0.039*
Hct decline (%)	4.94 ± 3.41	5.23 ± 3.55	0.695
Intraoperative blood loss (ml)	489.20 ± 239.72	641.40 ± 288.21	0.005*
Blood transfusion *n* (%)	2 (4%)	8 (16%)	0.046*
Duration of operation (min)	69.10 ± 27.52	67.90 ± 26.38	0.824
Weight of fibroids removed (g)	724.46 ± 289.91	805.64 484.76	0.312
Largest fibroid removed (cm)	8.06 ± 3.34	8.20 ± 3.78	0.845
Number of fibroids removed	2.32 ± 1.87	2.90 ± 1.25	0.278
Complication *n* (%)	0 (0)	0 (0)	–
Hospitalization (day)	2.20 ± 0.53	2.26 ± 0.56	0.587

BMI body mass index, *hct* hematocrit, *hgb* hemoglobin

*p value < 0.05

Table 2 Correlation between clinical variables and intraoperative blood loss

	Intraoperative blood loss	
	Correlation coefficient (r)	p
BMI	0.126	0.210
Oxytocin	−0.279	0.005
Operation time	0.579	0.000*
Size of the uterus in pelvic examination	0.578	0.000*
Number of fibroids removed	0.269	0.007*
Largest fibroid removed	0.428	0.000*
Weight of fibroids removed	0.595	0.000*

BMI body mass index

*p value < 0.05

Other common methods in combating bleeding is to inject vasoconstrictive substances into the fibroid tissue during surgery, but these methods require an additional step [6, 10, 22]. Another vasoconstrictive substance is a peptide hormone called oxytocin. Our study found that intravenous oxytocin infusion is an effective method in reducing blood loss, and it does not require any additional steps during the procedure.

Oxytocin is a hormone known for its role during delivery and lactation and has been used for over 100 years. Oxytocin was first discovered by Sir Henry Dale in 1906 and started its clinical use in 1909 by William Blair Bell. Synthetic oxytocin is now routinely used for the augmentation of labor and prevention of postpartum bleeding [23]. Oxytocin acts directly on the myometrium through the oxytocin receptor (OXTR) and stimulates contractions. Oxytocin receptors also exist in the nonpregnant uterus with a 50–100 times lower concentration [15]. The expression of oxytocin receptors have been identified in the endometrium as well as in the microvascular endothelial cells of the myometrium [24, 25]. Further, oxytocin receptors were found to be higher in fibroids than in normal myometrium [26].

One of the first studies on the use of oxytocin during myomectomies was conducted in 2005 [17]. An oxytocin infusion of 15 IU in 125 ml was administered to abdominal and vaginal myomectomy cases. The author reported that average blood loss during the surgery was similar in the oxytocin (508 ± 558 ml) and control groups (451 ± 336 ml). Wang et al. [27] used oxytocin infusion (10 IU in 1000 ml saline) at a rate of 120 ml/h in laparoscopic myomectomy cases. The oxytocin infusion during the surgery significantly reduced the intraoperative blood loss in their study cohort [27]. The IBL in the ocytocin group was 269.5 ± 225.8 and

Table 3 Multiple Regression analysis of factors associated with intraoperative blood loss during myomectomies

Dependent variable: intraoperative blood loss	Standardized coefficients (beta value)	95% confidence interval	*p* value
Oxytocin	−0.232	−201.10 to −51.64	0.001*
Operation time	0.253	0.63 to 4.55	0.01*
Size of the uterus in pelvic examination	0.047	−12.54 to 19.26	0.67
Number of fibroids removed	0.143	−6.76 to 36.19	0.17
Largest fibroid removed	0.235	−0.91 to 37.28	0.07
Weight of fibroids removed	0.256	0.02 to 0.33	0.02*

Adjusted $R^2 = 0.551$

*p value < 0.05

was 445 ± 268.6 in the control group [27]. A recent study on abdominal myomectomy cases also showed a reduction in bleeding during surgery as well as decreased need for transfusion [28]. The authors used 30 IU oxytocin in a 500 ml saline solution at a rate of 120 ml/h. The IBL was 189.5 ± 16.72 ml in the oxytocin group while it was 692.25 ± 89.93 ml in the control group [28]. The timing of oxytocin administration and dosages administered, may explain the differences among the various studies. Agostini et al. [17] administered oxytocin at the time of uterine incision, whereas, all of the other studies, including ours, administered oxytocin after the induction of general anesthesia prior to surgery. This might explain Agostini et al's findings that oxytocin did not show a significant reduction in bleeding while all other studies did show a reduction.

The distinctive feature of our study lies in the low dosage of oxytocin used during the myomectomy. We found that by administrating 10 IU oxytocin in a 500 ml saline solution significantly reduced intraoperative bleeding and did not present patients with significant side effects. The oxytocin infusion is also more practical and has fewer steps involved than the intramyometrial injection of substances. The studies on oxytocin use during myomectomies are summarized in Table 4. The strength of our randomized study is that it shows how oxytocin infusion is effective in decreasing intraoperative blood loss even at lower dosages.

Table 4 Studies on oxytocin use during myomectomies

	Oxytocin group	Control group	
Agostini et al. [17]	*N* = 47	*N* = 47	Oxytocin infusion was started with the uterine incision
Vaginal or abdominal myomectomy	15 IU in 125 ml over 30 min		
	Laparotomy: 32 Vaginal: 15	Laparotomy: 31 Vaginal: 16	No difference in terms of intraoperative blood loss
IBL	508 ± 558 ml	451 ± 336 ml	
Weight of fibroids removed	286 ± 206 g	268 ± 253 g	
Wang et al. [27]	*N* = 30	*N* = 30	Oxytocin was started after induction of anesthesia
Laparoscopic myomectomy	10 IU in 1000 ml saline at a rate of 120 ml/h	Saline	
IBL	269.5 ± 225.8 ml	445 ± 268.6 ml	Benefits (decreases IBL)
Weight of fibroids removed	208 ± 149.6 g	184.5 ± 127.5 g	
Atashkhoei et al. [28]	N = 40	*N* = 40	Oxytocin was started after the induction of anesthesia
Abdominal myomectomy	30 IU oxytocin in 500 ml saline at a rate of 120 ml/h	Saline	
IBL	189.5 ± 16.72 ml	692.25 ± 89.93 ml	Benefits (decreases IBL)
Our study (2018)	*N* = 50	*N* = 50	Oxytocin was started after the induction of anesthesia
Abdominal myomectomy	10 IU oxytocin in 500 ml of saline at a rate of 120 ml/h	Saline	
IBL	489.20 ± 239.72 ml	641.40 ± 288.21 ml	Benefits (decreases IBL)
Weight of fibroids removed	724.46 ± 289.91 g	805.64 ± 484.76 g	

IBL intraoperative blood loss

Apart from other studies we also analyzed factors contributing to intraoperative blood loss during myomectomies. Our study's limitation lies in the inability to include laparoscopic myomectomy cases, as there is a steep learning curve for these kinds of cases.

In conclusion, oxytocin infusion during myomectomies reduces intraoperative blood loss and the need for subsequent blood transfusion. The infusion of oxytocin may be an alternative method to lower blood loss during myomectomies. Further trials with different doses and administration protocols are needed to confirm these findings. Also, more data is needed on the application of oxytocin infusion in other gynecologic surgeries.

Authors contribution BAÇ: project development, manuscript writing, data analysis. BAM: project development, manuscript editing, data analysis. NK: data collection. AS: data collection. GD: methodology. TÇ: investigation.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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