

# Safety and efficacy of lidocaine plus epinephrine on intraoperative bleeding in abdominal myomectomy: A double-blind clinical trial

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## Abstract

**Background:** Uterine fibroid is a common benign pelvic tumor and abdominal myomectomy may cause excessive intraoperative bleeding, which may lead to adverse outcomes.

**Objective:** This study was planned to evaluate the effectiveness of the injection of lidocaine plus epinephrine to reduce intraoperative bleeding in abdominal myomectomy.

**Methods:** During October 2019 and May 2020, 60 eligible women with uterine fibroids were enrolled in a randomized controlled trial. Our patients were divided into two groups of lidocaine plus epinephrine defined as Group L and placebo defined as Group P. In group L, lidocaine 3 mg/kg plus 0.5 ml of adrenaline which reached to 50 cc with saline solution and in group P, 50 ml of normal saline was used. Both the combined solution and normal saline were infiltrated to the serous and myometrium above and around the fibroid before incision. Patients' demographic data, total operative time, hemoglobin changes, and the degree of surgical difficulty were evaluated and compared between the two groups.

**Results:** There was no significant difference between the two groups in terms of demographic data. Hemoglobin changes ( $p < 0.0001$ ) and the degree of surgery difficulty ( $p = 0.01$ ) were significantly lower in Group L compared with Group P. In each group the drop in hemoglobin levels from baseline to 4 h postoperatively was significant ( $p < 0.0001$ ). A significantly meaningful correlation was reported between hemoglobin changes and the degree of surgery difficulty with the size of the uterine and fibroids ( $p < 0.05$ ). While a negative correlation was found regarding gravidity and surgery difficulty ( $r = -0.413$ ,  $p = 0.02$ ). Surgery duration was longer in Group P compared with Group L  $70.66 \pm 19.85$  versus  $66.16 \pm 14.48$ , respectively, but with no significant difference ( $p = 0.32$ ). No significant adverse reaction or serious complication was reported in the two groups. Hemodynamic parameters were kept in the normal range throughout the surgery.

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**Conclusion:** A combination of lidocaine plus epinephrine during abdominal myomectomy appears to be a safe and effective method in reducing blood loss.

**KEYWORDS**

epinephrine acetate, hemorrhage, lidocaine hydrochloride, myomectomy, uterine fibroids

## 1 | INTRODUCTION

Uterine fibroids originate mostly from the myometrium and are one of the most common benign diseases during women's reproductive period. Fibroids are often asymptomatic but 20%–50% of cases complain from menorrhagia, constipation, urinary complaints, and pelvic pain and pressure. The severity of the symptoms depends on the size, location, and number of fibroids. In cases of infertility or severe and persistent anemia or intolerable symptoms, surgery is considered.<sup>1–3</sup> Based on the current evidence, an abdominal myomectomy is a classic and safe surgical method. However, intraoperative bleeding could be a life-threatening complication that is associated with poor hemostasis, trauma to feeding vessels, improper suturing due to inexperience of the surgeon, and also feature of fibroids.<sup>4,5</sup> Intraoperative bleeding in myomectomy leads to adverse consequences, including difficult and complicated operations, the need for transfusion, uterine rupture, and prolonged hospitalization.<sup>6</sup>

Despite the use of a variety of strategies, such as uterotonics, antifibrinolytics, vasoconstrictive agents, uterine artery dissection, embolization, and tourniquet, the optimal preoperative strategy for reducing blood loss during myomectomy is still unclear.<sup>4,6</sup> Vasopressin has been widely used in various gynecological procedures to reduce intraoperative hemorrhage, and it has been especially and effectively used in abdominal myomectomy.<sup>7,8</sup> Vasopressin has been widely available. However several related adverse effects have been reported particularly on the cardiovascular system<sup>9–12</sup> and the United States Food and Drug Administration has not approved the drug for this purpose.<sup>13</sup> A recent meta-analysis of 26 clinical trials concluded that it was not yet clear which intervention was optimal. This review also found that gravidity, size of the fibroids and duration of disease were among some influential factors. In addition utero-tonic agents combined with peripheral vasoconstrictors were more effective in controlling blood loss during abdominal myomectomy.<sup>14</sup> Therefore, searching for new horizons is crucial to finding novel, safe, and effective preventive strategies. The aim of this study was to investigate the effects of lidocaine plus epinephrine on intraoperative bleeding in abdominal myomectomy.

## 2 | PATIENTS AND METHODS

This randomized double-blind controlled clinical trial took place at Alzahra hospital, a referral and academic center affiliated with Guilan University of Medical Sciences (GUMS) between October 2019 and May 2020.

First, informed consent was obtained from all patients. Then their information, including demographic and medical record data, and medications were collected.

*Inclusion criteria:* Women 18–50 years old, candidate for an elective abdominal myomectomy, intramural fibroids >5 cm, and symptomatic fibroids. Pure myomectomy, not additional procedures such as excision of endometriosis.

*Exclusion criteria:* Pregnant and postmenopausal women, liver diseases, any contraindication to the studied drugs, malignancy, asthma, ischemic heart diseases, cardiomyopathy, congestive heart failure, hypertension, and pulmonary disease.

Eligible patients were randomly divided into two groups of lidocaine plus epinephrine (L) and placebo (P) based on randomization in blocks of four. All patients underwent standard general anesthesia and surgery protocols. Just before surgery, 2 g of ceftazolin was injected intravenously. In Group L, lidocaine 3 mg/kg (vial 100 mg/5 ml; Caspian Tamin) plus 0.5 ml of adrenaline (vial 1 mg/ml; Daru pakhsh) with saline solution reached 50 ccs and in Group P, 50 ml of normal saline were used. Both the combined solution and normal saline were infiltrated to the serous and myometrium above and around the fibroid before incision. The obstetrician and the responsible resident who completed the questionnaire were blinded to the study groups. However in order to intervene immediately, the anesthesiologist was aware of the groups types. To avoid intravascular injection, the solution was injected in the mentioned areas after an exact aspiration. Baseline hemoglobin values were measured and compared with four hours post operation to detect the severity of bleeding. To prevent the effects of some influencing factors, such as surgery methods and surgeon experiences on the results, all the operations were performed by a single surgeon. The degree of surgery difficulty was evaluated by using an index of 1–10 with the following divisions: 1–3 low difficulty, 4–6 intermediate difficulty, and 7–10 high difficulty.<sup>15</sup>

Hemodynamic parameters, including heart rate, systolic, and diastolic blood pressure were recorded in all cases. At the end of the surgery, all the samples were examined by a pathologist.

## 3 | SAMPLE SIZE

Based on the study of Zullo et al.<sup>16</sup> in which the amount of bleeding was  $144 \pm 48$  ml in the treatment group compared to  $213 \pm 51$  ml in the placebo group, a sample size of 30 patients in each group was considered sufficient.  $\alpha = 0.05$ ,  $\beta = 0.10$ ,  $S_1 = 48$ ,  $S_2 = 51$ ,  $d = 41$ .

$$\alpha = 0.05$$

## 4 | STATISTICAL ANALYSIS

The data were analyzed by SPSS version 21. Mann–Whitney *U* test, *t*-test,  $\chi^2$  test, and Spearman correlation test were used as well. Statistically, a *p*-value less than 0.05 was considered significant.

## 5 | ETHICAL CONSIDERATIONS

The study protocol was approved by the Research Ethics Committee of the Guilan University (ethical code: IR.GUMS.REC.1398.118) and also was registered in the Iranian registry of clinical trials as IRCT20090525001946N10.

## 6 | RESULTS

Finally, the data from 60 patients were analyzed. Patients' demographic data are presented in Table 1. There was no significant difference between the two groups in terms of American Society of Anesthesiologist class, age, parity, gravidity, body mass index, the number of fibroids, and uterine size ( $p > 0.05$ ) Table 1.

There was no significant difference between the two groups in terms of demographic data. Hemoglobin changes ( $p < 0.0001$ ) and the degree of surgery difficulty ( $p = 0.01$ ) were significantly lower in Group L compared with Group P. In each group, the drop in hemoglobin levels from baseline to 4 h postoperatively was significant ( $p < 0.0001$ ). A significantly meaningful correlation was reported between hemoglobin changes and the degree of surgery difficulty with the size of the uterine and fibroids ( $p < 0.05$ ). While a negative correlation was found regarding gravidity and surgery difficulty ( $r = -0.413$ ,  $p = 0.02$ ; Tables 2 and 3).

**TABLE 1** Patients' demographic characteristics in two groups

Variable	Condition	Lidocaine plus adrenaline		Placebo		Total		<i>p</i> value
		Number	%	Number	%	Number	%	
Age (years)	Less than 40	14	46.7	13	43.3	27	45	0.79
	More than 40	16	53.3	17	56.7	33	55	
Age (years) mean $\pm$ SD		42.6 $\pm$ 5.95		42.6 $\pm$ 7.15		42.6 $\pm$ 6.52		0.96
BMI (kg/m <sup>2</sup> )	Less than 19	1	3.3	1	3.3	2	3.3	0.95
	19–25	10	33.3	12	40	22	36.7	
	25–30	13	43.3	12	40	25	41.7	
	More than 30	6	20	5	16.7	11	18.3	
BMI (kg/m <sup>2</sup> ) mean $\pm$ SD		26.92 $\pm$ 5.61		27.15 $\pm$ 4.53		27.03 $\pm$ 5.06		0.86
ASA class	I	21	70	17	56.7	38	63.3	0.28
	II	9	30	13	43.3	22	36.7	
Gravidity	No pregnancy	10	33.3	9	30	19	31.7	0.712
	One	5	16.7	3	10	8	13.3	
	Two	4	13.3	7	23.3	11	18.3	
	Three or more	11	36.7	11	36.7	22	36.7	
(Gravidity) mean $\pm$ SD		1.93 $\pm$ 1.91		2.1 $\pm$ 1.93		2.02 $\pm$ 1.9		0.738
Parity	No children	10	33.3	8	26.7	18	30	0.68
	One child	6	20	4	13.3	10	16.7	
	Two children	7	23.3	11	36.7	18	30	
	Three children	7	23.3	7	23.3	14	23.3	
(Parity) mean $\pm$ SD		1.53 $\pm$ 1.5		1.77 $\pm$ 1.59		1.65 $\pm$ 1.53		0.561
Uterine size (mm <sup>2</sup> ) mean $\pm$ SD		8213.5 $\pm$ 3795.8		10,874.8 $\pm$ 8385.9		9544.2 $\pm$ 6591.6		0.119
Myoma size (mm <sup>2</sup> ) mean $\pm$ SD		5402.7 $\pm$ 3591.9		7461.1 $\pm$ 6345.5		6431.9 $\pm$ 5216.4		0.127
Duration of disease mean $\pm$ SD		3.16 $\pm$ 2.37		4.76 $\pm$ 7.58		3.96 $\pm$ 5.62		0.277

Abbreviations: ASA, American Society of Anesthesiologist; BMI, body mass index.

**TABLE 2** The trend of hemoglobin (Hb) changes inter and between groups from baseline to 4 h postoperation

Groups	Baseline	4 h Postoperation	Intergroups <i>p</i> value	Hb changes	<i>p</i> value
Lidocaine plus adrenaline	11.7 ± 1.26	11 ± 1.24	0.0001	0.7 ± 0.53	0.0001
Placebo	11.55 ± 1.33	9.18 ± 1.64	0.0001	2.37 ± 1.17	
<i>p</i> Value	0.65	0.0001			

**TABLE 3** Comparison of surgical difficulty between groups

Surgery difficulty degree	Lidocaine plus adrenaline		Placebo		Total		<i>p</i> value
	Number	%	Number	%	Number	%	
2	4	13.3	2	6.7	6	10	0.01
3	5	16.7	2	6.7	7	11.7	
4	6	20	3	10	9	15	
5	11	36.7	4	13.3	15	25	
6	3	10	5	16.7	8	13.3	
7	1	3.3	5	16.7	6	10	
8	0	0	4	13.3	4	6.7	
9	0	0	3	10	3	5	
10	0	0	2	6.7	2	3.3	
Total	30	100	30	100	60	100	

The duration of surgery in group P compared with group L was  $70.66 \pm 19.85$  versus  $66.16 \pm 14.48$  respectively, but the difference was not significant ( $p = 0.32$ ). In Group P, a positive correlation was observed between the size of fibroids ( $p = 0.04$ ) and uterus ( $p = 0.01$ ) with the surgical difficulty while it was not observed in Group L ( $p = 0.77$ ), ( $p = 0.45$ ), respectively (Table 4). No significant adverse reaction or serious complication was reported in the two groups. Hemodynamic parameters were kept within the normal range throughout the surgery. The consort flow diagram of the survey is shown in Figure 1.

## 7 | DISCUSSION

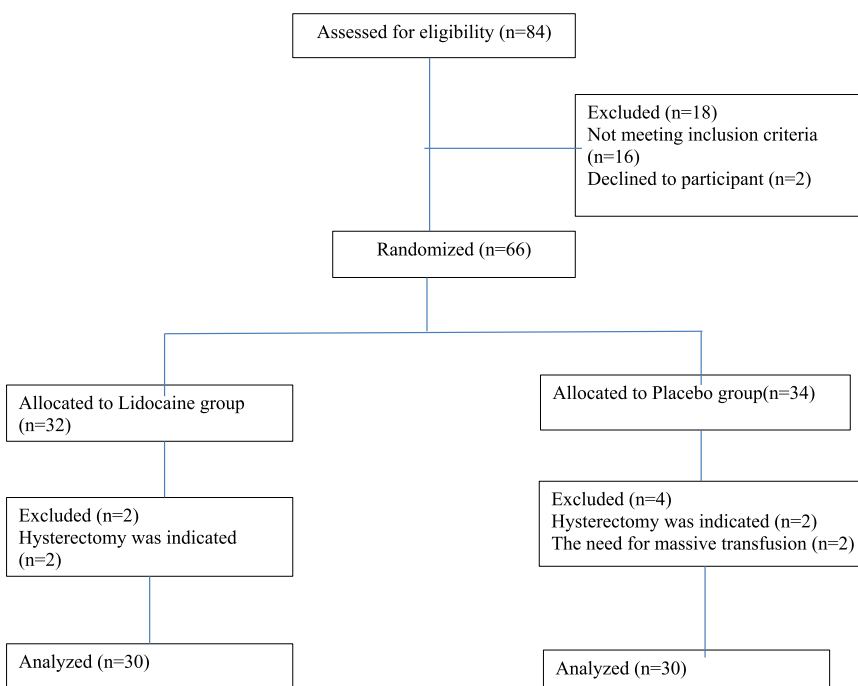
Despite pharmacological and nonpharmacological interventions, the problem of massive and sometimes unexpected hemorrhage still exists among those who have undergone abdominal myomectomy. It has also been reported that 20% of these cases require transfusion and in 2% of them, the surgical schedule is changed to hysterectomy.<sup>13</sup> In Takeda S study, a preoperative balloon catheter in the internal iliac artery was evaluated to reduce intraoperative bleeding in abdominal surgery.<sup>17</sup> Another drug that could effectively control bleeding during abdominal myomectomy was carbetocin, which is a long-acting analog of oxytocin. In fact, the potential risk of heavy bleeding during surgery and preventing strategies remains a major concern for both anesthesiologists and surgeons.<sup>18</sup> However, the

results of previous studies on the best option for this purpose are not consistent.<sup>14</sup> It has recently been argued that performing myomectomy by the preservation of the pseudocapsule results in less bleeding even in laparotomy. Zikopoulos et al.<sup>19</sup> showed that this method was associated with less bleeding and a faster healing process compared with conventional abdominal hysterectomy. In this study, we detected that lidocaine plus adrenaline could significantly reduce intraoperative blood loss. The degree of difficulty in Group L was also lower in the intervention group compared with Group P. Our results are very similar to the results found in studies on vasopressin, however, with no serious cardiovascular threatening effects. The lower degree of difficulty in Group L was probably due to less hemorrhage and better visualization of the surgical field. Another reason could be the contraction of myometrium around the fibroids. Epinephrine differs from vasopressin in its duration of action, indeed epinephrine induces vasoconstriction effects for 5–6 hours while the effects of vasopressin last 17–35 minutes.<sup>16</sup> Although it has positive effects on the state of blood loss, one hypothetical risk might be that this long duration of action results in tissue damage and ischemia. Although the vasoconstriction property of adrenaline results in a significant reduction in intraoperating hemorrhage, the risk of rebound bleeding exists shortly after surgery. Because the long-term vasoconstriction effects of adrenaline may lead to false and inadequate hemostasis during surgery. In fact, the reason for the addition of lidocaine to this solution was that the local vasodilator effects of this local anesthetic could partially counterbalance the

**TABLE 4** The correlation between hemoglobin (Hb) reduction, surgical difficulty, and some quantitative variables in two groups

Variables		Lidocaine and adrenaline injection Hb changes before and after surgery	Placebo injection Hb changes before and after surgery	Lidocaine and adrenaline injection Difficulty of surgery	Placebo injection Difficulty of surgery
Age (years)	Pearson correlation	-0.19	-0.23	-0.24	-0.24
	<i>p</i> value	0.29	0.23	0.18	0.18
Parity	Pearson correlation	-0.25	-0.04	-0.32	-0.08
	<i>p</i> value	0.17	0.83	0.07	0.67
Size of the uterus	Pearson correlation	0.05	0.39	0.14	0.42
	<i>p</i> value	0.76	0.03	0.45	0.01
Size of the fibroids	Pearson correlation	-0.04	0.51	-0.05	0.36
	<i>p</i> value	0.80	0.004	0.77	0.04
Duration of the disease	Pearson correlation	-0.04	-0.02	-0.07	0.30
	<i>p</i> value	0.83	0.91	0.69	0.10
BMI	Pearson correlation	0.08	0.008	-0.022	-0.0215
	<i>p</i> value	0.65	0.96	0.906	0.255
Gravidity	Spearman correlation	-0.31	0.02	-0.413	-0.059
	<i>p</i> value	0.09	0.91	0.023	0.765

Abbreviation: BMI, body mass index.

**FIGURE 1** CONSORT flow diagram of the survey

prominent vasoconstriction of adrenaline. Moreover, studies have clearly confirmed that local anesthetic infiltration at the site of surgery could eliminate the postoperation pain and the need for analgesics.<sup>20,21</sup> Several other studies have shown the promising effects of local anesthetic infiltration to reduce intra-operative

bleeding, however, the underlying mechanism is not yet well understood.<sup>22</sup> Of course, it should be noted that none of our cases were affected by this complication. A combination of a local anesthetic and adrenaline has also been used successfully in dental surgeries.<sup>23</sup> Bameshki et al.<sup>24</sup> also showed that local injection of bupivacaine and

epinephrine markedly reduced intraoperative bleeding in tonsillectomy. Couto et al.<sup>20</sup> observed a significant reduction in intraoperative bleeding with the combination of topical tranexamic acid plus lidocaine in facelift surgery.

However, searching the literature we found only two similar studies supporting the safety and efficacy of using a solution consisting of local anesthetic and adrenaline in gynecological surgeries.<sup>13,16</sup> Lidocaine has been known as a safe local anesthetic with rare life-threatening reactions.<sup>25</sup> Considering several advantages of the combination of a vasoconstrictor to local anesthetics,<sup>26</sup> epinephrine was added to lidocaine. Epinephrine is the most commonly used vasoconstrictor acting through stimulation of  $\alpha_1$ -adrenergic receptors in arteriole walls.<sup>27</sup> In a supporting study, Zullo et al.<sup>16</sup> investigated the effects of bupivacaine added to adrenaline, which was injected into the myometrium overlying the fibroids. They found that in the experimental group, no patient needed a transfusion, and surgery duration and blood loss were also significantly lower compared with the placebo group. Their inclusion criteria were similar to ours; however, their patients underwent laparoscopy myomectomy. In addition, they evaluated the severity of postoperative pain, which was significantly lower in the bupivacaine group.

In line with our study, Hudecek R et al. evaluated the efficacy and safety of epinephrine 12  $\mu$ g with articaine as local anesthetic in laparoscopic myomectomy. They reported that this combination could significantly reduce the amount of bleeding during surgery, duration of surgery, and length of hospital stay. Similar to the present study none of the patients in the two studies mentioned above were affected by serious adverse effects. In summary, the evidence regarding the issue is limited so further research is required to answer the question of whether the administration of adrenaline added to local anesthetics is superior to adrenaline alone. In fact, this study revealed promising findings, supporting the efficacy of a safe, cost-effective, available, and easy-to-use intervention. However, further studies should address several unanswered questions about the choice of local anesthetics, the optimal dosage, the most effective method and timing of drug administration, and certain cases that benefit most from this intervention.

## 8 | CONCLUSION

This study demonstrated that the administration of a saline solution containing lidocaine and adrenaline in abdominal myomectomy could be considered an effective and safe method. To find practical results which could be generalized to a clinical setting, more well-planned trials with larger sample sizes and more details are highly recommended. Certainly more confirmatory studies can be planned based on these promising results.

## 9 | STRENGTHS

In this study for the first time, the efficacy and safety of the combination of lidocaine with adrenaline was assessed in blood loss reduction during myomectomy.

## 10 | LIMITATION

Obviously, this paper provided valuable data, but some limitations should be considered. It was a single-center study with a small sample size and in addition to hemoglobin level changes and surgery difficulty, more factors could be assessed.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### AUTHOR CONTRIBUTIONS

**Mandana Mansour-Ghanaei, Gelareh Biazar:** Conceptualization. **Mandana Mansour-Ghanaei, Gelareh Biazar, Fatemeh Noori:** Data collocation. **Seyed Mohammad Asgari-Ghalebini:** Formal Analysis. **Seyede Hajar Sharami, Mandana Mansour-Ghanaei, Fatemeh Hosseinzadeh:** Writing-review and editing. **Fatemeh Noori:** Writing-original draft.

### DATA AVAILABILITY STATEMENT

Related data of this project are available on request.

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**How to cite this article:** Mansour-Ghanaei M, Hosseinzadeh F, Sharami SH, Biazar G, Noori F, Asgari-Ghalebini SM. Safety and efficacy of lidocaine plus epinephrine on intraoperative bleeding in abdominal myomectomy: a double-blind clinical trial. *Health Sci Rep.* 2022;5:e551. doi:10.1002/hsr2.551