ORIGINAL ARTICLE

EFFICACY AND SAFETY OF SUBLINGUAL MISOPROSTOL IN REDUCING INTRAOPERATIVE BLOOD LOSS DURING ABDOMINAL MYOMECTOMY

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ABSTRACT

Objective: To compare the effectiveness and safety of 400 mg of sublingual and per rectal Misoprostol when given 1 hour prior to abdominal Myomectomy in reducing intraoperative blood loss.

Material and Methods: A quasi-experimental study involving women with uterine leiomyoma was conducted at Khyber Teaching Hospital, Peshawar, Pakistan, including patients who underwent abdominal myomectomy. Participants were enrolled after providing informed consent and were randomly assigned to either group 1, which received 400 mg of misoprostol rectally, or group II, which received 400 mg of misoprostol sublingually one hour before surgery. A total of 48 participants were enrolled. The primary outcome measures were intraoperative blood loss and the difference between preoperative and postoperative hemoglobin levels; secondary measures included postoperative febrile morbidity, gastrointestinal complaints, and other side effects. All data were stored and analyzed using SPSS 20. A p-value of <0.05 was considered statistically significant.

Results: The mean age of patients in the per rectal group 1 was 32.6 (± 4.8) years, and in the sublingual group 2 it was 33.8 (± 4.5) years. The mean parity in group 1 was 1.8 (1.3), while in group 2 it was 1.3 (1.2). The mean uterine size in group 1 was 17.6 (2.3) cm, and in the per rectal group 15.8 (2.2) cm. Blood loss during the myomectomy procedure was 342.8 (154.6) ml in group 1 and 386.5 (118.3) ml in the sublingual group. Complications of misoprostol were very rare and minor, such as nausea and uterine cramps.

Conclusion: Sublingual misoprostol is an effective and safe agent for reducing blood loss during abdominal myomectomy. When compared with the use of the same dose of per rectal misoprostol given 1 hour before surgery, it did not show a significant difference; however, the ease of administration via the sublingual route is favored and acceptable to women in the Asian community.

Keywords: Sublingual Misoprostol, Intraoperative Blood Loss, Myomectomy

This article may be cited as: Mazhar T, Ghayur MS, Adil Z, Haris A. Efficacy And Safety Of Sublingual Misoprostol In Reducing Intraoperative Blood Loss During Abdominal Myomectomy. J Med Sci 2026 January - March;34(1):10-15

INTRODUCTION

Uterine myomas are the most common tumors that develop from the smooth muscles of the myometrium and occur in about 20-40% of women of reproductive age. These tumors are estrogen-dependent and are mostly asymptomatic but become symptomatic in 20-50% of cases, presenting with menorrhagia, chronic pelvic pain, and urinary or bowel symptoms. [1, 2] The severity of symptoms depends on the size, number, and location of the tumors. The standard treatment for fibroids is hysterectomy for women who have completed their families, and myomectomy for those who wish to conceive. Bleeding is a common complication of the myomectomy procedure, with 20% of patients requiring a transfusion. Various methods are used to reduce bleeding, including GnRh agonist use before surgery, intraoperative vasopressin, intravenous oxytocin, intramyometrial bupivacaine with epinephrine, tourniquet application, and pre-operative uterine artery embolization. [3, 4]

Misoprostol, a PGE1 analogue, is used not only for managing miscarriages, inducing labor, and preventing and treating primary postpartum hemorrhage but also has gained significance in myomectomy. It enhances myometrial contractions, which helps reduce blood flow through the uterine arteries. Misoprostol decreases bleeding through two mechanisms. [5] First, it increases myometrial contractions because prostaglandins affect vascular structures supplied by both the uterine artery and

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Date Received: 30/11/2025
Date Revised: 27/03/2026
Date Accepted: 30/03/2026

utero-ovarian anastomoses, causing vascular contraction and lower blood flow. The second mechanism involves the direct vasoconstrictive effect of misoprostol on uterine arteries.

MATERIALS AND METHODS

This study was conducted in the Gynecology and Obstetrics unit of Khyber Teaching Hospital from 1st September 2021 to 31st August 2023. It is a quasi-experimental study in which patients who attended the outpatient clinic for treatment of symptomatic myomas and met the inclusion criteria were included.

Inclusion criteria included patients aged 20-40 years, all fibroids classified as intramural or subserosal by ultrasound, and a uterine size smaller than 24 weeks of gestation on bimanual examination. Exclusion criteria consisted of patients with a history of previous pelvic surgery, laparotomy, or C-section, a history of endometriosis, allergy to misoprostol, cardiac or pulmonary diseases, bleeding or coagulation disorders, Hemoglobin levels below 10 gm, chronic endocrine or metabolic diseases like diabetes, and a BMI greater than 30.

The goal of my study was to assess the effect of a single sublingual dose of misoprostol 400 mg given 1 hour preoperatively and to compare it with the same dose given rectally on the amount of bleeding during abdominal myomectomy. Primary outcome measures included the amount of intraoperative blood loss, the difference between pre-op and post-op hemoglobin levels, and the need for intraoperative or post-op blood transfusions. Secondary measures included postoperative febrile morbidity, other side effects, and complications of surgery. Efficacy was evaluated based on decreased blood loss during myomectomy surgery, postoperative hemoglobin levels at 6 and 24 hours, and the necessity for intraoperative and postoperative blood transfusions. Safety was assessed by monitoring side effects associated with sublingual misoprostol, such as fever, chills, vomiting, diarrhea, or vaginal bleeding immediately prior to surgery.

All patients were counseled about the study. Written informed consent was obtained after explaining the possible consequences. A detailed history was taken from all women, and they underwent a clinical examination to rule out general medical disorders. Abdominal and vaginal examinations were conducted. Abdominal and pelvic ultrasounds were performed to assess the number, location of fibroids, and the largest fibroid diameter. Preoperative full blood count and coagulation profile tests were conducted for all women. Surgery was performed by the same surgical team to eliminate any bias related to surgical skill. The myomectomy procedure involved enucleating all myomas and clamping large blood vessels; no other interventions, such as tourniquets or ligation, were used. Intraoperative blood loss was measured by collecting and weighing surgical sponges before and after surgery, then converting the weight to blood volume, considering 1 gram of blood as equivalent to 1 mL. Blood loss was further estimated by measuring the amount of blood collected in a suction bottle at the end of surgery and the blood in the kidney trays when blood-soaked packs were squeezed into them. The blood on the surgical drapes and the pooled blood beneath the patient and on the floor were also noted. The volume of irrigation fluid was subtracted from the final blood loss volume. Vital data during the operation, including duration of surgery and the time from opening of the peritoneum to closure, were recorded. Hemoglobin levels were measured at 6 hours and 24 hours postoperatively, and any intraoperative or postoperative blood transfusions were documented. The number and size of fibroids were recorded after surgery. Any postoperative side effects, such as febrile episodes, shivering, or diarrhea within 24 hours post-surgery, were also documented.

All data were stored and analyzed using SPSS 20. Descriptive statistics were calculated for quantitative variables such as age, parity, mean fibroid size, and mean Hb concentration. Frequencies and percentages were calculated for categorical variables like efficacy and side-effect frequency. Efficacy in both groups was stratified by age, parity, fibroid size, pre- and post-surgery Hb concentration, and blood loss during surgery. A post-stratification chi-square test was used to compare the efficacy of the two groups, with a p-value < 0.05 considered significant. All results are presented in tables and graphs.

RESULTS

In the study, 24 women were randomized to receive 400 mg of rectal misoprostol, and 24 women were given sublingual 400 mg misoprostol 1 hour before myomectomy.

The baseline demographic characteristics, including age, parity, preoperative and postoperative hemoglobin, and uterine size, are shown in Table 1.

In one case, the procedure resulted in a hysterectomy. She was para 3 with fibroids in the broad ligament and posterior uterine wall. Despite performing internal iliac ligation, the bleeding persisted, leading to a total abdominal hysterectomy as a last resort.

DISCUSSION

Ahmad Abbas compared the efficacy of 400 micrograms of sublingual and rectal misoprostol administered one hour before abdominal myomectomy. He found that the mean blood loss in the rectal group was 247.44 ± 106.04 ml, compared to 256.17 ± 116.27 ml in the sublingual group ($P = 0.06$). No significant differences were observed between the two groups in the change in hemoglobin levels and hematocrit values pre- and postoperatively

Table No 1: Baseline Demographic and Intraoperative Blood Loss Comparison.

Treatment Group Statistics					
Variables	Rectal Mean (SD) Group 1	Sublingual Mean (SD) Group 2	t (df=46)	P value	Effect Side Hedges Correction
Age	33.8 (4.5)	32.6 (4.8)	0.87	0.391	0.25
Parity	1.3 (1.2)	1.8 (1.3)	-1.16	0.254	-0.33
Uterine size in Cm	15.8 (2.2)	17.6 (2.8)	-2.37	0.022	-0.69
Pre op Hb (g%)	11.7 (0.6)	12 (0.4)	-2.22	0.032	-0.63
Blood loss during surgery	342.8 (154.6)	386.5 (118.3)	-1.10	0.277	-0.31
Post op Hb (g%)	10.8 (0.3)	11 (0.2)	-2.67	0.010	-0.76
No of Fibroids	1.8 (1)	2.5 (1.3)	-2.39	0.021	-0.68
Hb difference	0.9 (0.6)	1 (0.5)	-0.79	0.436	-0.22

Table No 2: Side Effects, Complications, frequency of blood transfusions in Both Groups

Side Effects of Misoprostol	Side Effects of Misoprostol	Group 2 (Sublingual N-24)
Uterine bleeding	**-**	-
Uterine cramps	-	1
Nausea	-	1
Vomiting	-	-
Diarrhea	-	-
Shivering	-	-
Complications and frequency of blood transfusions		
Intraoperative blood transfusions		
1 Transfusion	9	4
> 1 Transfusion	7	5
Post-operative blood transfusions	3	2
Procedure ending in hysterectomy	1	-

($P < 0.05$). Similarly, there were no differences in patients' demographics, duration of surgery ($P = 0.9$), or need for transfusion ($P = 0.08$). Both groups showed similar results regarding the occurrence of adverse effects ($P = 0.97$). Fever and chills were the most common adverse effects, indicating that both rectal and sublingual misoprostol 400 mcg are equally effective in reducing blood loss during abdominal myomectomy. [6] In our study, the mean blood loss was 342 ± 154 mL in the rectal group and 386 ± 118 mL in the sublingual group ($P = 0.27$).

In another study, Ahmad Abbas compared two different doses of Misoprostol. He administered 200 and 400 mcg of sublingual misoprostol and observed that the estimated blood loss was significantly lower in the misoprostol 400 mcg group (373.3 ± 55.6 vs 560 ± 105.2 ml, $P < 0.001$). Moreover, the reduction in hemoglobin level was significantly less in the misoprostol 400 mcg group (0.8 ± 0.18 vs 1.7 ± 0.38 gm/dL, $P < 0.001$). The operative duration was significantly shorter in the misoprostol 400 mcg group (91.3 ± 5.7 vs 111.2 ± 6.3 minutes, $P < 0.001$. [7] In our study, post-op hemoglobin 24 hours after surgery was 11 (0.2) gm% in the sublingual group and 10.8(0.3) gm% in the per rectal group, with a p-value of 0.10.

Lima Wetherell conducted a double-blind RCT pilot study in Melbourne, Australia, and compared sublingual misoprostol 400 mg with placebo preoperatively. Intraoperative blood loss in the misoprostol group was 306 ml ± 281 ml, compared to 325 ml ± in the placebo group ($P = 0.83$). Fibroid volume was a consistent predictor of intraoperative blood loss. For each ml increase in fibroid volume, there was an associated increase in blood loss by 0.25ml (95% CI: 0.07-0.46). [8] In our study, the mean uterine size was 17.6 (2.8) cm in the sublingual group and 15.8 (2.2) cm in the per rectal group, p value 0.022.

The most popular method for reducing hemorrhage in myomectomy is the use of GnRH analogues. However, myoma growth recurs after treatment is stopped. Osteoporosis also occurs with long-term use of GnRH analogues. Therefore, its use is limited to decreasing intraoperative blood loss. Additionally, GnRH analogues are expensive, and their hemorrhage-reducing effect takes

time to manifest, whereas misoprostol is given an hour before surgery and significantly decreases intraoperative blood loss. [9, 10]

In comparison between misoprostol and vasopressin, cost and safety concerns are present. Side effects have been reported to arise from the use of local vasopressin. Temporary increase in blood pressure during local vasopressin injection, bleeding at the injection site, and intravascular infiltration by mistake can lead to pulmonary edema or myocardial infarction. [10, 11]

The mechanical vascular occlusion technique known as a tourniquet or uterine artery embolization has also gained popularity in recent years. These methods all require additional intervention or a separate procedure. The challenges of accessing the uterine arteries in large, laterally positioned myomas, such as broad ligament myomas, and the difficulty of placing tourniquets are disadvantages. Julian conducted a systematic review and meta-analysis of 2016 patients to identify non-hormonal interventions, perioperative interventions, and devices to reduce blood loss during surgery for uterine leiomyomas. She found that perioperative use of misoprostol was associated with a lower postoperative hemoglobin drop (0.39 versus 0.59 gm%, $p<0.1$). [12,13]

The route of misoprostol administration affects the onset, duration of action, the effects achieved, and the severity of side effects. The oral and sublingual routes produce the quickest and strongest uterotonic effects compared to vaginal and rectal routes, but they also come with more side effects. [14-16]

The onset of action for oral, sublingual, and vaginal routes occurs within 30 minutes, while the rectal route takes longer at 100 minutes. The sublingual route reaches the highest peak plasma concentration and systemic bioavailability, whereas vaginal and rectal routes provide more sustained plasma levels. All routes have an action duration of at least 2 hours, which is sufficient for an uncomplicated open myomectomy. El Maraghay compared 400 mg of sublingual misoprostol with a placebo 60 minutes prior to myomectomy. Postoperative blood loss, hemoglobin levels, and hospitalization time were reduced (252.5 ± 170.5 ml, 10.8 ± 1.02 g/dl, and 1.8 ± 0.4 days, respectively) ($P = 0.003$, 0.032, and 0.004, respectively). [17]

Asma Hunain and Mohammad Khalaf observed changes in the vascularity and perfusion of fibroids by studying Doppler blood flow patterns. The study included 82 patients, with 41 in each group.

Women were randomly assigned to group A, which received 400 mg of misoprostol rectally, and group B, which received the medication sublingually one hour before surgery. The vascularization of the fibroid and surrounding myometrium was visualized using color Doppler. There was no statistically significant difference in RI, PI, or systolic-diastolic ratios at different times of assessment between the two groups. Misoprostol significantly reduces the vascularity and perfusion of fibroids, regardless of whether it was administered rectally or sublingually one hour prior to the procedure. R1 was 0.90 ± 0.11 in the rectal group versus 0.85 ± 0.19 in the sublingual group ($P = 0.07$) at 20 and 40 minutes after intake. [18]

Sabry found that, with the use of 400 mg Misoprostol transrectally one hour prior to surgery, intraoperative blood loss was significantly lower than with placebo, at 460.8 ± 155 ml versus 815.4 ± 187.7 ml, $P < 0.00001$. The duration of the operation was also significantly shorter: 70.84 ± 11.3 minutes versus 87.6 ± 21.2 minutes, $P < 0.001$. Postoperative hemoglobin levels showed a significant difference (10.6 ± 0.96 versus 9.76 ± 0.78). The decrease in hemoglobin percentage was significantly lower in the misoprostol group compared to the other group (1.16 ± 0.5 g/dl versus 1.7 ± 0.5 g/dl, $P = 0.005$). [19]

The dosage and route of administration of misoprostol vary across published studies. Some researchers found no statistical difference in mean blood loss or postoperative hemoglobin levels after surgery.

This may be due to the smaller sample sizes in these studies. Although the direct impact of sublingual misoprostol has not been widely studied, [20-22] a study by Mansoureh involved 64 patients undergoing abdominal myomectomy who were randomized into two groups: one receiving 200 mg of sublingual misoprostol 30 minutes before surgery, and the other receiving a placebo. The mean age, BMI, and baseline hemoglobin levels showed no significant differences; however, hemoglobin levels 6 hours after surgery were significantly higher in the misoprostol group (Hb 9.8 ± 0.8 versus 9.1 ± 0.9, $P = 0.003$). [23, 24]

Ivanzzo found no significant differences between groups in site or number of myomas, but there was a notable difference in myoma size. The mean fibroid size in the misoprostol group was 33.8 ± 15.2 cm compared to 24 ± 13.6 cm in the control group, $P = 0.042$. Postoperative Hb was 10.8 g ± 1.02 g/dL in the misoprostol group versus 9.9 ± 1.3 g/dL in the other group. Blood loss in the two groups was 336 ± 160.9 ml, respectively, $P = 0.077$. [25] The use of misoprostol during cervical myomectomy may not provide the same benefits as its ability to decrease cervical resistance, but further studies are needed.

We had four patients with cervical and intramural fibroids, not isolated cervical fibroids. In these cases, bleeding was significantly reduced with misoprostol. However, in one patient with multiple intramural and cervical fibroids, the procedure resulted in hysterectomy due to intractable bleeding.

CONCLUSION

Sublingual misoprostol is an effective and safe option for reducing blood loss during abdominal myomectomy. When compared with the same dose of per rectal misoprostol given 1 hour before surgery, blood loss during the procedure and the change in HB were similar. P values of 0.277 and 0.436, respectively, showed no significant difference; however, the ease of administration via the sublingual route is preferred and acceptable to women in the Asian community.

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26. This study was approved by the Institutional Research and Ethical Review Board of Khyber Teaching Hospital, Peshawar, Pakistan vide no. 89/DE/KMC dated: 24/08/2021

CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE: NIL

Authors Contribution:

Following authors have made substantial contributions to the manuscript as under

Authors	Conceived & designed the analysis	Collected the data	Contributed data or analysis tools	Performed the analysis	Wrote the paper	Other contribution
Mazhar T	✓	✓	×	×	✓	×
Ghayur MS	✓	×	✓	✓	✓	×
Adil Z	✓	✓	×	×	×	✓
Haris A	✓	×	✓	✓	✓	×

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical Approval:

This Manuscript was approved by the Ethical Review Board of Khyber Teaching Hospital, Peshawar, Pakistan
Vide No. 89/DME/KMC. Dated: 24 08 2021