ORIGINAL ARTICLE

EFFICACY OF PREOPERATIVE MISOPROSTOL IN REDUCING HEMORRHAGE DURING ABDOMINAL MYOMECTOMY

Qudsia Qazi Khan, Nazia Liaqat, Tanveer Shafqat, Shandana Bawar

Department of Gynaecology & Obstetrics, Lady Reading Hospital Peshawar-Pakistan

Background Uterine myomas are most common non-cancerous tumours in reproductive period. The fertility preserving surgery, i.e., myomectomy as compared to hysterectomy, is associated with massive blood loss due to dissection of huge fibroids making it technically difficult procedure. Misoprostol (a uterotonic) is an effective option amongst different interventions used to reduce intraoperative blood loss during myomectomy. This randomized control trial investigated effectiveness of single dose of rectal misoprostol given preoperatively in reducing intraoperative blood loss during abdominal myomectomy. **Methods** Fifty Patients undergoing abdominal myomectomy were selected for the study. Twenty-five patients were given 800 micrograms misoprostol per rectally half an hour before surgery while rest received placebo, i.e., control group. Number and weight of surgical packs were recorded both Pre and post operatively to assess blood loss. Preoperative and 24 hrs postoperative haemoglobin was also recorded. Data analysed by SPSS-20. **Results:** Mean of age, parity and myoma size were not statistically different between the two groups. However intraoperative blood loss (as measured by weighing and counting number of swabs used) and postoperative haemoglobin after 24 hours were significantly different between two groups with *p*-value <0.01. **Conclusion:** Single dose of misoprostol given preoperatively via rectal route is effective in reducing intraoperative blood loss during abdominal myomectomy. Misoprostol must be used in different doses and routes in order to investigate its effectiveness in reducing intraoperative blood loss.

Keywords: Preoperative misoprostol; Abdominal myomectomy; Intra operative; Blood loss

Citation: Khan QQ, Liaqat N, Shafqat T, Bawar S. Efficacy of preoperative misoprostol in reducing haemorrhage during abdominal myomectomy. J Ayub Med Coll Abbottabad 2020;32(2):198–203.

INTRODUCTION

Uterine fibroids are most common benign tumours (15–30%) of female pelvis in reproductive age group, i.e., one in every 5 women may have fibroids during their childbearing age, commonly seen in women over 30 yrs. Myomas are composed of smooth muscles and connective tissue. They are mostly asymptomatic but 20–50% of them cause menstrual disorders badly affecting quality of life. Myomas are also associated with pelvic pain or pressure, infertility, colorectal and urinary complaints. The standard treatment of symptomatic fibroids is hysterectomy but other treatment options are also available such as uterine artery embolization, myolysis and myomectomy. The most common conservative, i.e., fertility preserving surgical procedure used is abdominal myomectomy.[1]

Myomectomy can be performed via hysteroscopy, laparoscopy and laparotomy. Abdominal myomectomy has short term complications including haemorrhage, pyrexia and visceral damage while long term complications are thrombo embolism and infection. Significant blood loss associated with removal of huge fibroids makes myomectomy a technically challenging procedure for gynaecologists despite advances in techniques for reducing haemorrhage during the procedure. Reports suggest that blood transfusion is needed in up to 20% and hysterectomy in up to 2% of patients undergoing abdominal myomectomy.[2] Since myomectomy is an elective procedure so careful planning and considered use of some of the interventions to arrest haemorrhage can avoid need for blood transfusion and postoperative anemia.[3]

Medical agents are always an attractive option to arrest haemorrhage. Three categories of interventions to control haemorrhage are being identified.

(a) interventions on uterine arteries as peri cervical mechanical tourniquet, preoperative clamping or embolization of bilateral uterine and/or ovarian arteries (UAE)[4]

(b) uterotonics as ergometrine, oxytocin, misoprostol, intraoperative vasopressin or terlipressin injection (hormonal tourniquet) into myometrium.

(c) myoma dissection techniques as use of laser, electrosurgery and chemical dissectors such as mesna.[4–6,11]

(d) GnRH analogues reduce haemorrhage during surgery if used for 2–4 months preoperatively. GnRH analogues are expansive and may make removing fibroids difficult because of reduced distinction between capsule and myometrium.[12]

There are always controversies among gynaecologists for choosing the best method with minimal adverse effects and cost along with availability and effective results because types of these interventions are so varied. Vasopressin is not a cost-effective choice and there can be associated pulmonary oedema, temporary increase in blood pressure and myocardial infarction with it. Evidence suggests that myometrial concentration of oxytocin receptors is very low in non-pregnant uteri, making oxytocin less useful.[5,13]

Preoperative Misoprostol, a prostaglandin E1 analogue, was registered in many countries for use in gynaecology and obstetrics, i.e., evacuation of uterus during the 1980s. Its popularity in developing countries is accounted by its advantages over other interventions as being inexpensive choice with thermal and light stability and shelf life of several years in tropical conditions.11 It acts by promoting myometrial contractions and reducing uterine artery blood flow significantly and thus reducing bleeding during myomectomy.[7,10] Misoprostol has advantage of multiple routes of administration as sublingual, oral, rectal or vaginal. Misoprostol acid levels peak within 1 hour after rectal administration and it persists for up to 6 hours at substantially higher concentrations in plasma, i.e., for the extent of the surgical procedure during those crucial minutes after surgery.[15] than when administered orally or sublingually.[8]

Side effects of misoprostol appear within 90 minutes of administration, i.e., while patient is under anaesthesia and are less disturbing in nature. Single rectal dose of misoprostol is associated with lower incidence of shivering and hyperpyrexia and with no serious systemic side effects.[16]

A number of interventions that are used to reduce intraoperative blood loss during myomectomy, have been investigated in different trials regarding their safety and effectiveness. We selected investigation of the effectiveness of single preoperative dose (800 ug) of misoprostol given rectally in reducing intraoperative blood loss during abdominal myomectomy in a larger subset of patients than previously studied in Turkey.[14]

MATERIAL AND METHODS

In this study, fifty patients with symptomatic fibroids were enrolled amongst those attending gynaecology outpatient clinic at Lady Reading Hospital Peshawar from July 2017 to December 2018. All patients with following inclusion criteria were included (i) patients over 18 years of age, (ii) mean uterine fibroid size of 5–15 cm (ii) 1–5 symptomatic fibroids on sonography report (iii) with abnormal uterine bleeding, dull lower abdominal pain, subfertility and recurrent miscarriages. Abdominal myomectomy was planned for all of these patients according to set protocols of our department.

Patients with a history of pelvic infection, known allergy to prostaglandins, pelvic or ovarian endometriosis, bleeding disorders and use of anticoagulation were excluded. Any patient using hormonal therapy preoperatively such as GnRH analogues or oral contraceptive pills was excluded as these drugs can affect intraoperative bleeding or duration of operation. Information sheet having nature and possible consequences of study explained in understandable form was given to all patients. A written informed consent was obtained. The protocol of this study was approved by institutional review board of hospital ethical committee.

Randomization of patients was done into two groups using a computer-generated random table and sealed envelopes were prepared according to it**.** Drug was administered by interns according to envelop number. Both surgeons and patients were kept unaware about nature of drug being prescribed to all patients. Code was broken at the end of study to see the assigned treatment received by each patient. Patients were then grouped and compared into two groups as those receiving preoperative rectal dose of 800 ug of misoprostol half an hour before surgery (Group A) and those receiving placebo before surgery (Group-B).

Detailed history, complete abdominal and vaginal examination and preoperative investigations including complete blood count, blood group, Hepatitis profile, coagulation profile and trans abdominal ultrasound were done.

Standard technique of performing abdominal myomectomy via transverse lower abdominal incision was used in all patients by same team of consultants without use of intra operative tourniquet. All surgeons tried to remove fibroids by using minimum number of incisions given either anteriorly or posteriorly. In both groups the size and number of myomas were recorded after removing all myomas.

Intraoperative blood loss was measured by collecting and weighing surgical sponges both pre and post operatively and then converting weight with volume of blood loss as [post-operative wet sponge weight in (grams) minus preoperative dry sponge weight (grams) which means 1 ml of blood weighs 1 gm. Haemoglobin levels were measured 24 hours before and after surgery. Full post-operative observational chart including pulse, blood pressure, temperature, fluids intake, urine output and need for blood transfusion was maintained.

Data was registered in collection forms including (a) sociodemographic and clinical characteristics (b) the size and number of myomas (c) primary outcome measures as intraoperative blood

loss in millilitres, operative time (measured from incision of first myoma to serosal closure of last myoma wound), and (d) haemoglobin concentration 24 hours pre and post operatively, need for blood transfusion postoperatively.

Statistical analysis of data of this study was done by using recent version of SPSS software. Differences in rates were compared using chi-square test while student T test was used to compare means and standard deviations. The difference in blood loss in a sample of women treated with misoprostol vs placebo was primary outcome measure of the study. The *p*-value < 0.05 was considered significant.

RESULTS

A total of 50 cases were included in the study. Table-1 describes basic demographic characteristics of patients as age, parity and size of myomas which were not significantly different between the groups. All patients had multiple uterine fibroids located at different sites of uterus (submucous, intramural and subserous)

The main presenting complaint of both groups was menstrual irregularity including both heavy menstrual bleeding (HMB) and abnormal uterine bleeding (AUB) as seen in 52% of cases followed by pelvic pain as shown in table-2.

Intraoperative blood loss was significantly lower in women receiving rectal misoprostol as compared to placebo group as shown in table-3. Additionally, the drop in postoperative haemoglobin concentration was significantly less in misoprostol group compared with the placebo group (*p*-0.04). In group A with misoprostol the mean blood loss was 328 mls ±SD 149 compared to 484 mls ± SD 188 in placebo group. Mean postoperative Haemoglobin, measured 24 hours after surgery, was 10.36±SD 1.09 with misoprostol compared to 9.7± SD 1.03 as shown in Table-3 (*p*-0.002). In placebo group, five patients required blood transfusion, having haemoglobin of <8, postoperatively compared to one transfusion with misoprostol group. Not more than two blood transfusions were required for both groups of patients.

The mean duration of surgery was significantly shorter in group-A (25.9 vs 34.3 min) compared to group B. In group-A 64% patients had <40 minutes of surgery compared to 20% in placebo group table-5.

Table-1: demographic characteristics of sample (Group Statistics)

	Type of Agent	n	Mean
Age	Misoprostol	25	32.4
	Placebo	25	32.8
Parity	Misoprostol	25	1.2
	Placebo	25	1.9
Myoma Size	Misoprostol	25	69.1
	Placebo	25	54.7

Table-2: Presenting complaints of sample

			Type of Agent	
			Misoprostol	**Placebo**
HMB	Yes	Count	9	4
		n %	36.0%	16.0%
	No	Count	16	21
		n %	64.0%	84.0%
Dysmenorrhoea	Yes	Count	3	0
		n %	12.0%	.0%
	No	Count	22	25
		n %	88.0%	100.0%
Pain	Yes	Count	8	4
		n %	32.0%	16.0%
	No	Count	17	21
		n %	68.0%	84.0%
AUB	Yes	Count	4	10
		n %	16.0%	40.0%
	No	Count	21	15
		n %	84.0%	60.0%
Sec. Amenorrhoea	Yes	Count	1	0
		n %	4.0%	.0%
	No	Count	24	25
		n %	96.0%	100.0%
Infertility	Yes	Count	3	4
		n %	12.0%	16.0%
	No	Count	22	21
		n %	88.0%	84.0%
Pressure symptoms	Yes	Count	0	2
		n %	.0%	8.0%
	No	Count	25	23
		n %	100.0%	92.0%
Urinary Retention	Yes	Count	1	1
		n %	4.0%	4.0%
	No	Count	24	24
		n %	96.0%	96.0%

Table-3: Intraoperative blood loss

	Type of Agent	n	Mean	*p*-value
Preop Haemoglobin	Misoprostol Placebo	25 25	11.7 11.2	.25100
Postop Haemoglobin	Misoprostol Placebo	25 25	10.3 9.7	.04300
Blood Loss (in ml)	Misoprostol Placebo	25 25	328.4 484.8	.00200

Table-4: Secondary outcome measures

Outcome	Agent	n	Mean
Preop Haemoglobin	Misoprostol	25	11.7
	Placebo	25	11.2
Postop Haemoglobin	Misoprostol	25	10.3
	Placebo	25	9.7
Postop Transfusion	Misoprostol	25	0.3
	Placebo	25	0.6
Hospital stay	Misoprostol	25	4.2
	Placebo	25	4.2

Table-5: Duration of surgery

			Type of Agent		Total
			Misoprostol	**Placebo**	
Duration of Surgery	**<40**	Count	16	5	21
		% within Type of Agent	64.0%	20.0%	42.0%
	>40	Count	9	20	29
		% within Type of Agent	36.0%	80.0%	58.0%
Total		Count	25	25	50
		% within Type of Agent	100.0%	100.0%	100.0%

DISCUSSION

Open myomectomy remains the principal treatment for symptomatic fibroids in sub-Saharan countries with significant intraoperative haemorrhage. The complications and burden of this haemorrhage are even greater in resource-limited settings. Fletcher in 1996 reported that 23% patients undergoing open myomectomy lost over 1000ml of blood.[9] Other studies reported the operative blood loss range between 100 ml and 3000 mls.[2]

Although blood loss at open myomectomy remains dreary with the use of various pharmacologic agents yielding inconclusive results but pre-operative prostaglandins, have offered a more reliable and realistic hope in resource-limited settings. Few studies done have demonstrated its safety and efficacy and larger multicentre trials are further recommended. The bioavailability curve of rectal and vaginal misoprostol is qualitatively similar although rectal route has longer half-life with lesser side effects than oral route.

The results of this study showed benefits of single preoperative dose of rectal misoprostol, a readily available uterotonic, in reducing intra-operative blood loss (IBL) by at least 20%, i.e., about 101mls. In our study mean blood loss with misoprostol was 328 mls as compared to 484 mls with placebo. Our results are comparable with those of Naib J Showing 15–18% reduction (370 mls vs 310 mls) in blood loss with misoprostol (17). Celik H reported a reduction in blood loss by 149 ml, i.e., mean loss was 621 mls with placebo compared to 472 mls with misoprostol. The effectiveness of misoprostol in reducing IBL during abdominal myomectomy is also evident in another study by Ishrat S et al and Cochrane database.[5,18]

In our study operative time was also reduced with misoprostol and these findings were consistent with those of Celik.[14] In our study operative time was < 40 minutes in 64% pts of misoprostol group while in a study by Celik mean operative time was 48.5 minutes for misoprostol compared to 58 min for placebo group.[14]

Women undergoing myomectomy are usually young with few co morbidities and have the ability to replace lost haemoglobin with intravenous iron and blood transfusion in moderate to severe anaemia. In the current study the difference between pre- and post-operative haemoglobin values was less in misoprostol group (11.7 VS 10.3 gm %) than with placebo (11.2 VS 9.7 Gm%). Our results are consistent with those of Mansoureh reporting that 24 hrs postoperative haemoglobin was not significantly different between the two groups (10.50±0.56 vs 10.24±0.58, p=0.066).[19,20]

Our study showed that misoprostol is associated with reduced but statistically insignificant need for postoperative blood transfusion thus reducing post-operative complications and length of stay in hospital. Blood transfusion was advised only after taking into consideration the 24 hours postoperative haemoglobin. Our results are comparable with those of Naib et al and Celik H showing blood transfusions in 33.3% cases of placebo VS 15.3% cases of misoprostol group.[14,17]

The beauty of our agent is no need for additional intraoperative procedures. Tourniquet occlusion of uterine and ovarian vessels prior to myomectomy was reported by Kongenyuy *et al* to have higher efficacy in reducing intraoperative blood loss when compared to other interventions. Mechanical vascular occlusion techniques such as tourniquet or uterine artery embolization, though popular in recent years have significant disadvantages as (i) require additional interventions or a separate procedure during the operation (ii) difficulty of access to the uterine artery with large and laterally placed myomas and (iii) difficulty of placing the tourniquet.[7,21]

In this study no difference has been found in terms of 24 hrs postoperative haemoglobin, anaemia, need for blood transfusion and hospital stay, consistent with results of Tang.[16]

Our study has limitations as it was a single centre study involving evaluation of only one route of administration with small sample size and misoprostol was not compared with other currently used methods.

Open myomectomy remains the principal treatment for symptomatic fibroids in sub-Saharan countries with significant intraoperative haemorrhage. The complications and burden of this haemorrhage are even greater in resource-limited settings. Fletcher in 1996 reported that 23% patients undergoing open myomectomy lost over 1000ml of blood.[9] Other studies reported the operative blood loss range between 100 ml and 3000 mls.[2]

Although blood loss at open myomectomy remains dreary with the use of various pharmacologic agents yielding inconclusive results but pre-operative prostaglandins, have offered a more reliable and realistic hope in resource-limited settings. Few studies done have demonstrated its safety and efficacy and larger multicentre trials are further recommended. The bioavailability curve of rectal and vaginal misoprostol are qualitatively similar although rectal route has longer half-life with lesser side effects than oral route.

The results of this study showed benefits of single preoperative dose of rectal misoprostol, a readily available uterotonic, in reducing intra-

operative blood loss (IBL) by at least 20%, i.e., about 101 mls. In our study mean blood loss with misoprostol was 328 mls as compared to 484 mls with placebo. Our results are comparable with those of Naib J Showing 15% to 18% reduction (370 mls vs 310 mls) in blood loss with misoprostol.[17] Celik H reported a reduction in blood loss by 149 ml, i.e., mean loss was 621 mls with placebo compared to 472 mls with misoprostol. The effectiveness of misoprostol in reducing IBL during abdominal myomectomy is also evident in another study by Ishrat S *et al* and Cochrane database.[5,18]

In our study operative time was also reduced with misoprostol and these findings were consistent with those of Celik.[14] In our study operative time was < 40 minutes in 64% pts of misoprostol group while in a study by Celik mean operative time was 48.5 minutes for misoprostol compared to 58 min for placebo group.[14]

Women undergoing myomectomy are usually young with few co morbidities and have the ability to replace lost haemoglobin with intravenous iron and blood transfusion in moderate to severe anaemia. In the current study the difference between pre- and post-operative haemoglobin values was less in misoprostol group (11.7 VS 10.3 gm%) than with placebo (11.2 VS 9.7 Gm%). Our results are consistent with those of Mansoureh reporting that 24 hrs postoperative haemoglobin was not significantly different between the two groups (10.50±0.56 vs 10.24±0.58, p=0.066) (19,20).

Our study showed that misoprostol is associated with reduced but statistically insignificant need for postoperative blood transfusion thus reducing post-operative complications and length of stay in hospital. Blood transfusion was advised only after taking into consideration the 24 hours postoperative haemoglobin. Our results are comparable with those of Naib et al and Celik H showing blood transfusions in 33.3% cases of placebo VS 15.3% cases of misoprostol group.[14,17]

The beauty of our agent is no need for additional intraoperative procedures. Tourniquet occlusion of uterine and ovarian vessels prior to myomectomy was reported by Kongenyuy *et al* to have higher efficacy in reducing intraoperative blood loss when compared to other interventions. Mechanical vascular occlusion techniques such as tourniquet or uterine artery embolization, though popular in recent years have significant disadvantages as (i) require additional interventions or a separate procedure during the operation (ii) difficulty of access to the uterine artery with large and laterally placed myomas and (iii) difficulty of placing the tourniquet.[7,21]

In this study no difference has been found in terms of 24 hrs postoperative haemoglobin, anaemia, need for blood transfusion and hospital stay, consistent with results of Khan R.[13]

Our study has limitations as it was a single centre study involving evaluation of only one route of administration with small sample size and misoprostol was not compared with other currently used methods.

CONCLUSION

Single dose 800 mcg rectal Misoprostol given 30 minutes preoperatively during open myomectomy is effective in reducing intra-operative blood loss by at least 20% as measured by surgical mops and suction.

RECOMMENDATIONS

Large multicentre trials (with larger sample size, applying two routes of administration) should be conducted to investigate effectiveness of safer and cost-effective method, i.e., pre-operative misoprostol in reducing IBL within resource limited settings. These studies will also contribute to the body of knowledge on use of misoprostol that will guide formation of national and local health protocols and policies. UAE and GnRH analogues may be prohibitive in low income countries where necessary technology may not be available

AUTHORS' CONTRIBUTION

QQK: literature search, conceptualization of study design and write-up. NL: Data Collection. TS: Data analysis, interpretation. SB: Data analysis, proof reading.

REFERENCES

1. Parker WH. Uterine myomas: management. Fertil Steril 2007;88(2):255–71.
2. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev 2001;(2):CD000547.
3. LaMorte AI, LaIwani S, Diamond MP. Morbidity associated with abdominal myomectomy. Obstet Gynaecol 1993;82:897–900.
4. Negh N, Belli A, Morgan R, Manyodal. Pre-myomectomy uterine embolization minimizes operative blood loss. Br J Obstet Gynaecol 2004;111(10):1139–40.
5. Kimura T, Kusui C, Matsumura Y, Ogita K, Isaka S, Nakajima A. Effectiveness of hormonal tourniquet by vasopressin during myomectomy through vasopressin Via receptor ubiquitously expressed in the myometrium. Gynaecol Obstet Invest 2002;54(3):125–31.
6. Liu W, Tzeng C, YI-Jen C, Wang P. Combining the uterine depletion procedure and myomectomy may be useful for treating symptomatic fibroids. Fertil Steril 2004;82(1):205–10.
7. Amato P, Roberts AC. Transient ovarian failure (a complication of uterine artery embolization). Fertil Steril 2001;75(2):438–9.

8. Choksuchat C. Clinical use of misoprostol in nonpregnant women: Review article. J Minim Invasive Gynaecol 2010;17(4):449–55.
9. Fletcher H, Frederick J, Hardie M, Simeon D. A randomized comparison of vasopressin and tourniquet as hemostatic agents during myomectomy. Obstet Gynecol 1996;87(6):1014–8.
10. Allen RMO, Brien B. Uses of misoprostol in obstetrics and gynaecology. Rew Obstetrics Gynecol 200;2(3):159–68.
11. Higgins JPT, Green S, Cochrane Collaboration, editors. Cochrane handbook for systematic reviews of interventions. Chichester, England; Hoboken, NJ: Wiley-Blackwell, 2008; p.649.
12. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids (systematic review). Cochrane Menstrual Disord Subfertility Group Cochrane Database Syst Rev 2004;3.
13. Khan RU, EI- Rafaey H, Sharma S, Sooranna D, Stafford M. Oral, rectal, and vaginal pharmacokinetics of misoprostol. Obstet Gynaecol 2004;103(5 Pt 1):866–70.
14. Celik H, Sapmaz E. Use of a single preoperative dose of misoprostol is efficacious for patients who undergo abdominal myomectomy. Fertil Steril 2003;79(5):1207–10.
15. Zieman M, Fong SK, Beniwitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral and vaginal administration. Obstet Gynaecol 1997;90(1): 88-92
16. Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 2002;17(2):332–6.
17. Naib JM, Naveed P, Fatima S. Pre-operative use of misoprostol in major gynaecological surgeries. J Med Sci 2013;21(4):171–3.
18. Ishrat S, Islam F. Misoprostol in obstetrics and gynaecology-A clinical review. J Dhaka Med Coll 2009;18(1):75–8.
19. Vahdat M, Kashanian M, Asadollah S, Yazdkhasti P, Nikravan N. The effect of misoprostol on intraoperative blood loss after myomectomy. Int J Reprod Contracept Obstet Gynaecol.2017;4(3):776–9.
20. Browning RM, Trentino K, Nathan EA, Hashemi N. Preoperative anemia is common in patients undergoing major gynaecological surgery and is associated with fivefold increased risk of transfusion. Aust N Z J Obstet Gynaecol 2012;52(5):455–9.
21. Kongnyuy EJ, Winsonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. Cochrane Database Syst Rev 2014;8:CD005355.

Submitted: 19 May, 2019	*Revised: 16 October, 2019*	*Accepted: 27 October, 2019*

Address for Correspondence:

Nazia Liaqat, Department of Gynaecology & Obstetrics, Lady Reading Hospital Peshawar-Pakistan
Email: kamrantnk@gmail.com