The Efficacy of Vasopressin Versus Misoprostol for Reducing Blood Loss During Myomectomy Operation

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Abstract

Background: Uterine fibroid is considered the commonest non-cancerous uterine tumour. Myomectomy is a uterine-sparing approach that includes fibroids removal without uterine affection. It has been demonstrated that the estimated blood loss (EBL) during myomectomy ranges between 200 and 400 ml. Intramyometrial vasopressin injections during myomectomy might efficiently reduce the blood loss intraoperatively. Misoprostol might reduce intraoperative haemorrhage in myomectomy when haemorrhage represents an essential challenge.

Aim: Assessment of the efficiency of vasopressin versus misoprostol for reducing blood loss during myomectomy operation.

Methods: This single blinded randomized controlled trial (RCT) was conducted on 2 groups, group (1) enrolled 60 patients administrate 400 ug of presurgical rectal misoprostol 30 minutes before surgery and group (2) enrolled 60 patients administrate one ampule of vasopressin (20 units) by perivascular injection nearby vessels in the broad ligament prior to the myomectomy operation.

Results: Our current work showed that there was no significant relationship between number of fibroids and intraoperative blood loss, also no significant relation between maximum diameter of fibroid and intraoperative blood loss. No significant difference was detected between Vasopressin and misoprostol group regarding intraoperative blood loss and requirement for blood transfusion (BT). A significant relation was demonstrated between number of fibroid and hemoglobin (HB) level, hematocrit (HCT) level, MCV and MCH pre and post treatment in both groups and HB level, hematocrit level, MCV and MCH decrease in post than pretreatment.

Conclusion: In the context of myomectomy operation, vaginal misoprostol could be efficient as vasopressin in decreasing blood loss. A statistically significant difference of operation type was detected between different types of fibroids in both groups. Hysterectomy was more frequent in submucous group.

Keywords: Uterine Fibroids, Myomectomy, Vasopressin, Misoprostol, Blood Loss.

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INTRODUCTION

Uterine fibroids are considered the commonest non-cancerous uterine tumours. Their clinical presentation is diverse and may involve pelvic masses, pelvic pain, infertility and obstetric adverse events [1]. In addition, leiomyomas are the most frequent benign pelvic tumours in females, although prevalence may be underestimated secondary to asymptomatic females [2]. The proper management of leiomyomas aims to release the manifestations, the need for fertility, the need to keep the uterus, the possibility of accomplishing therapeutic aims, and general health conditions. Therapeutic modalities enhance leiomyoma- associated symptoms by decreasing leiomyoma size, managing leiomyoma- associated AUB, or conclusively curing the leiomyomas. The management includes several therapeutic modalities that involve medications, interventional radiology (IR), and surgical approaches [1].

Myomectomy is a uterine-sparing approach that includes fibroid removal without uterine affection. It is typically recommended to patients who hope to become fertile in the future, but it is also an option for people who are done having children and would like to keep their uterus [3]. The average volume of blood loss during myomectomy is about 300 ml, with blood loss more than one liter considered as major blood loss. Postsurgical blood loss may be associated with hypovolemia and coagulation changes [4].

Intra-myometrial vasopressin injection during myomectomy could efficiently reduce the operative bleeding and requirement for BT and cause a minimal drop in HB and HCT in the postsurgical period [5]. Misoprostol, used in birth induction and in the management of postpartum haemorrhages, could also reduce intraoperative haemorrhage in terms of myomectomy operations when haemorrhage represents an essential problem [6]. So, we aimed to compare the efficiency of vasopressin versus misoprostol in reducing blood loss in the context of myomectomy.

PATIENTS AND METHODS

This study was prospective single blinded RCT and was held at Obstetrics and Gynecology department, Mansoura University Hospitals, Mansoura University, Egypt from June 2021 to June 2022 after obtaining the approval from institutional review board (IRB). This study was conducted on two groups, group (1) included 60 patients took 400 ug of presurgical rectal misoprostol 30 minutes before surgery and group (2) included 60 patients took a single vial of vasopressin (20 units diluted in 20 ml of normal saline (NaCl 0.9%)). Perivascular injection was done nearby vessels in the broad ligament prior to the myomectomy.

This study included cases aged between 18 to 40 years, patient complaining of heavy menstrual bleeding, patient complaining of abdominal swelling due to multiple fibroid, patient refused hysterectomy and patient needed future fertility, but we excluded patients with age > 40 years, patient with hypersensitivity to the drug, and patient refused myomectomy.

Methods

Every patient was subjected to full history taking including demographic data (age, gender, residence), present history to establish their symptoms (bleeding, pain and swelling as well as their fertility status). A presurgical assessment was conducted to confirm that there were no medical situations that contraindicated the use of either vasopressin or misoprostol. General examination included blood pressure, heart rate, and temperature. Abdominal examination included size of the uterus by weeks, clinical examination, pelvic examination and bimanual examination for size of the uterus. Laboratory investigations such as CBC, coagulation profile, and liver and kidney function tests were also performed. Diagnosis of fibroid was done by

TVS and MRI. Data collection was done by analyst not participating in the study.

Procedure

The ward's interns administered drugs, and the surgeons conducting the procedures were unaware of who had taken the medication. The interns weren't contributing to the post-surgical management of the cases. The surgeons were instructed to restrict the incision numbers as possible. If essential, hysterectomy was conducted for adverse events, which include blood loss greater than three liters. Uterine incisions were sutured in three layers by utilizing polyglactin sutures. The leiomyomas were weighed, and the largest diameter was assessed.

Assessment of blood loss was done through lab investigations (HB and HCT before and after surgery), weight of towels and pampers before and after surgery plus suction plus any drop of blood on the floor of field, and by assessment of BT Surgical sponges and laparotomy packs were weighed dry prior to operation and wet directly following usage. Blood loss in the sponges was measured by the next formula: [wet sponge weight (gram)-dry sponge weight (gram)] divided by 1.06g/mL. The drapes nearby the surgical field were enclosed with laparotomy packs so that they absorbed no blood, confirming that all blood loss was assessed. The collected blood collected form the aspirator was evaluated with a graduated cylinder at the end of the surgery. Every irrigation was measured in advance and subtracted from the suction container's total contents.

Outcomes

The primary outcome comprised the rate of blood loss (the amount of blood lost from abdominal wall incision and uterine incision and closure); the secondary outcomes included rate of hysterectomy (number of patients who had hysterectomy); operation time (time from opening peritoneum till closure of peritoneum again); and rate of BT (transfusion of blood intraoperatively or postsurgically). Core body temperature more than 38 °C could be described as febrile morbidity.

Statistical Analysis

The gathered data was processed and analyzed using SPSS program. The proper statistical tests were utilized when required. P value less than 0.05 (5%) was considered significant.

Ethical Consideration

Study design was approved by IRB of Faculty of Medicine at Mansoura University. Informed verbal consent was obtained from all participated subjects. Confidentiality was respected. Collected data wasn't used for any other purpose. Subjects had the right to leave the study at any time.

RESULTS

There was no significant difference between both groups concerning age (p=0.092), gravidity (p=0.251), parity (p=0.741), medical history (p=0.810), surgical history (p=0.838), contraception use (p=0.168) and main complaints (p=0.093) in Table (1).

There was no significant difference between both groups concerning number of fibroid and fibroid maximum diameter and all types of tumour except for submucous type that demonstrates significant higher prevalence among Misoprostol than Vasopressin group (15 % versus 3.3%, respectively) in Table (2).

There was no significant relation between number of fibroids and intraoperative blood loss (p=0.795), also no significant relation between maximum diameter of fibroid and intraoperative blood loss (p=0.232), there was no significant difference was detected between Vasopressin and misoprostol group concerning Intra operative blood loss (p=0.09) and need for BT (p=0.679). A significant difference was detected between studied groups concerning operation type (p<0.001) in Table (3).

There was no significant relation between

number of fibroid and HB level, hematocrit level, MCV and MCH pre and post treatment. There was a statistically significant decrease in HB level, hematocrit level, MCV, and MCH, after treatment as compared to pretreatment value within each of the studied groups (number of fibroid) in Table (4).

There was no relation between maximum diameter of fibroid and HB level, hematocrit level, MCV and MCH pre and post treatment. Significant decreases were recorded in HB level, hematocrit level, MCV and MCH after treatment as compared to pretreatment value within each of the studied groups (maximum diameter of fibroid) in Table (5). .

There was no significant relation between types of fibroid and the following, HB level, hematocrit level, MCV and MCH pre and post treatment. For submucous tumour, there was a statistically significant decrease in HB level after treatment as compared to pretreatment value ($p<0.001$), hematocrit value ($p<0.001$), MCV ($P<0.001$) and MCH ($P<0.001$). For Intramural tumour, there was a statistically significant decrease in HB level after treatment as compared to pretreatment value ($p=0.037$), MCV ($P=0.01$) and MCH ($P=0.006$). For Subserous tumour, there was a statistically significant decrease in MCV after treatment as compared to pretreatment value ($p=0.025$) in Table (6).

There was no significant difference between studied groups concerning intraoperative blood loss ($p=0.059$). A significant difference of operation type was detected between different types of fibroid ($p=0.003$). Hysterectomy was more frequent among submucous group in Table (7).

Table (1): Demographic characteristics of the studied groups

	Vasopressin group N=60	Misoprostol group N=60	Test of significance
Age / years Mean±SD	36.18±3.79	34.85±4.76	t=1.69 p=0.092
Gravidity Median (min-max)	2(0-13)	1(0-14)	Z=1.15 P=0.251
Parity Median (min-max)	1(0-6)	1(0-5)	Z=0.330 p= 0.741
Medical history -ve +ve	50(83.3) 10(16.7)	49(81.7) 11(18.3)	X^2=0.06 P=0.810
Surgical history -ve +ve	43(71.7) 17(28.3)	44(73.3) 16(26.7)	X^2=0.042 P=0.838
Contraception use -ve +ve	50(83.3) 10(16.7)	55(91.7) 5(8.3)	X^2=1.91 P=0.168
Main complaint Swelling Pain Infertility H.M.B. R.P.L Metrorrhagia	6(10) 5(8.3) 21(35) 23(38.3) 1(1.7) 4(6.7)	4(6.7) 10(16.7) 15(25) 18(30.0) 0 13(21.7)	MC=9.44 P=0.093

t:Student t test, Z:Mann Whitney U test, X^2 :Chi-Square test, MC:Monte Carlo test

Table (2): Tumour type among studied groups

Site	Vasopressin group N=60	Misoprostol group N=60	Test of significance
Broad ligament	1(1.7)	2(3.3)	FET=0.342 P=1.0
Cervical	2(3.3)	1(1.7)	FET=0.342 P=1.0
Intramural	0	3(5.0)	FET=3.08 P=0.244
Fundal	19(31.7)	15(25.0)	X^2=0.657 P=0.418
Posterior wall	25(41.7)	20(33.3)	X^2=0.889 P=0.346
Low corporal	5(8.3)	3(5.0)	X^2=.536 P=0.464
Anterior wall	16(26.7)	10(16.7)	X^2=1.77 P=0.184
Subserous	1(1.7)	4(6.7)	FET=1.88 P=0.364
Submucous	2(3.3)	9(15.0)	X^2=4.90 P=0.027*
Number of fibroid One 2-3 ≥4	 41(68.3) 13(21.7) 6(10.0)	 51(85.0) 4(6.7) 5(8.3)	MC=5.94 P=0.051
Maximum diameter <5 5-7 >7	 11(18.3) 32(53.3) 17(28.3)	 20(33.3) 20(33.3) 20(33.3)	X^2=5.63 P=0.06

MC: Monte Carlo test, FET: Fisher exact test, X^2 :Chi-Square test, *statistically significant

Table (3): Intraoperative blood loss and requirement for BT according to number of fibroid, maximum diameter of fibroid and between studied groups

	Number of fibroid			**Test of significance**
	One (N=92)	2-3 (N=17)	>7 (N=11)	
Intra operative blood loss(mm)	462.67±85.21	474.12±125.22	479.55±119.97	F=0.230 p=0.795
	Maximum diameter			
	<5 (N=31)	5-7 (N=52)	>7 (N=31)	
Intra operative blood loss(mm)	446.77±99.01	466.44±90.12	480.97±95.98	F=1.11 P=0.232
		Vasopressin group (N=60)	**Misoprostol group (N=60)**	
Intra operative blood loss(mm)		451.02±72.98	480.67±110.39	t=1.74 p=0.09

Blood transfusion -VE +VE	 58(96.7) 2(3.3)	 56(93.3) 4(6.7)	X^{2FET}=0.702 P=0.679
Operation type Open Lap Hysterectomy	 55(91.7) 5(8.3) 0	 50(83.3) 0 10(16.7)	 Mc=15.23 P<0.001*

F:One Way ANOVA test, t:Student t test, MC; Monte Carlo test, FET :Fisher exact test *statistically significant

Table (4): Laboratory findings according to number of fibroid

		Number of fibroid			Test of significance
		One (N=92)	2-3 (N=17)	>7 (N=11)	
HB (gm/dl)	**Pre**	11.13±0.57	11.15±0.62	10.86±0.65	F=1.17 P=0.315
	After	10.45±0.51	10.39±0.55	10.17±0.54	F=1.44 P=0.240
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	
HCT	**Pre**	36.08±2.14	35.71±2.26	36.0±2.93	F=0.199 P=0.820
	After	31.62±2.78	31.12±2.23	31.81±2.93	F=0.444 P=0.643
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	
MCV	**Pre**	86.29±8.29	84.29±6.08	86.51±10.45	F=0.444 P=0.643
	After	79.90±7.01	78.06±4.69	79.45±8.56	F=0.516 P=0.598
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	
MCH	**Pre**	26.21±2.37	25.67±1.84	26.51±2.91	F=0.506 P=0.604
	After	22.45±2.01	21.77±1.86	22.40±2.49	F=0.809 P=0.448
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	

F:One Way ANOVA test, *statistically significant

Table (5): Laboratory findings according to maximum diameter of fibroid

		Maximum diameter of fibroid			Test of significance
		<5 (N=31)	5-7 (N=52)	>7 (N=31)	
HB	**Pre**	11.19±0.63	11.13±0.63	11.02±0.48	F=0.728 P=0.485
	After	10.57±0.60	10.39±0.52	10.32±0.42	F=1.97 P=0.145
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	

HCT	**Pre**	36.48±1.95	35.85±2.56	35.87±1.88	F=0.899 P=0.410
	After	32.37±3.38	30.98±2.42	31.73±2.32	F=2.71 P=0.071
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	
MCV	**Pre**	87.67±6.94	84.52±8.33	86.79±8.82	F=1.68 P=0.190
	After	81.71±6.18	78.12±6.39	79.92±7.68	F=2.81 P=0.065
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	
MCH	**Pre**	26.38±2.26	25.97±2.27	26.24±2.56	F=0.317 P=0.729
	After	23.03±1.78	21.97±1.98	22.29±2.19	F=2.76 P=0.07
Paired t test		**P<0.001***	**P<0.001***	**P<0.001***	

F:One Way ANOVA test, *statistically significant

Table (6): Relation between types of fibroid and complete blood count among studied cases

		Types			**Test of significance**
		Submucous	Intramural	Subserous	
HB (gm/dl)	**Pre**	11.30±0.60	11.0±0.356	10.50±0.424	F=1.92 P=0.190
	After	10.74±0.51	10.28±0.32	9.90±0.14	F=3.65 P=0.057
Paired t test		**P<0.001***	**P=0.037***	**P=0.205**	
HCT	**Pre**	36.78±1.48	35.0±2.0	37.50±2.12	F=2.03 P=0.174
	After	33.78±2.68	33.0±3.37	33.0±1.42	F=0.140 P=0.871
Paired t test		**P<0.001***	**P=0.161**	**P=0.205**	
MCV	**Pre**	88.89±8.29	92.25±10.40	97.0±4.24	F=0.793 P=0.475
	After	83.44±7.33	85.5±10.34	84.50±4.95	F=0.093 P=0.912
Paired t test		**P<0.001***	**P=0.01***	**P=0.025***	
MCH	**Pre**	26.78±2.73	28.25±2.87	28.0±2.83	F=0.457 P=0.644
	After	23.78±1.78	23.5±2.08	23.50±0.71	F=0.043 P=0.958
Paired t test		**P<0.001***	**P=0.006***	**P=0.205**	

F:One Way ANOVA test, *statistically significant

Table (7): Comparison of operative data between tumour subtypes

	Submucous	Intramural	Subserous	Test of significance
Intra operative blood loss(mm)	423.33±27.83	505±88.12	492.5±81.32	F=3.62 P=0.059
Operation type Open Hysterectomy	1(11.1) 8(88.9)	4(100) 0	2(100) 0	Mc=11.42 P=0.003*

MC:Monte Carlo test, F:One Way ANOVA test, *statistically significant

DISCUSSION

The aim of our study was to assess the efficiency of vasopressin versus misoprostol for reducing blood loss during myomectomy operations. We conducted a RCT on 2 groups: Group (1): 60 patients received 400 ug of presurgical rectal misoprostol half an hour before surgery. Group (2): 60 patients received a single vial of vasopressin (20 units in one ml), which was diluted in 20 ml of NaCl 0.9%. This was injected peri vascularly around vessels in the broad ligament prior to the myomectomy. Our data showed no significant difference between studied groups concerning age (p=0.092), obstetric history (p>0.05), medical history (p=0.810), surgical history (p=0.838), contraception use (p=0.168) and main complaints (p=0.093).

A study included 200 cases undergoing laparoscopic myomectomy who were divided into three groups: group 1 (50 cases) received vaginal misoprostol 400 mg 120 minutes prior to surgery, group 2 (100 cases) received intramyometrial injection of vasopressin (20 IU/100 mL diluated in NaCl 0.9%), and group 3 (50 cases) received no hemostatic agent. The three studied groups demonstrated insignificant differences concerning both parity and BMI [7].

Srivastava et al., compared the efficiency of intramyometrial vasopressin together with rectal misoprostol with intramyometrial vasopressin only to diminish blood loss throughout minimally invasive myomectomy. The basal sociodemographic charactarsistics of fibroids were similar in both groups [8].

Our study illustrated that there was no significant difference between the studied groups regarding number of fibroids, fibroid maximum diameter, and all types of tumours except for submucous type, which demonstrates statistically significant higher prevalence among Misoprostol than Vasopressin group (15% versus 3.3%, respectively). Protopapas et al., demonstrated that concerning features of leiomyomas, the average maximum diameter of the largest leiomyoma didn't vary significantly among the three studied groups. In addition, the fibroid numbers didn't vary significantly between all the studied groups. Significant increases in the percentages of solitary fibroids were recorded in groups 1 and 3 compared to group 2. The three groups had comparable ratios of ≥4 multiple leiomyomas. Intergroup comparisons demonstrated insignificant differences. The distribution of leiomyomas based on the FIGO classification was at comparable ratios among the three groups [7].

Our work demonstarted that there is no significant relationship between number of fibroids and intraoperative blood loss (p=0.795), also no statistically significant relation between maximum diameter of fibroid and intraoperative blood loss (p=0.232). No significant difference was determined between Vasopressin and misoprostol group concerning operative blood loss (p=0.09) and need for BT (p=0.679). A significant difference was detected between studied groups concerning operation type (p<0.001).

In Protopapas et al., concerning the leiomyo-

ma numbers, it was demonstrated that when 2–3 tumours were excised, estimated blood loss was significantly increased in the misoprostol compared to the vasopressin group. Such change was reversed (in other words, more in the vasopressin group) when ≥4 leiomyomas were excised (P<0.05). Comparison between groups 1 and 3 displayed a significant difference in estimated blood loss in the number subgroup ≥4 (P<0.05) [7].

Moreover, estimated blood loss (EBL) didn't differ significantly between the first and the second groups concerning the size subgroup (P = 0.697). In contrast, comparison between the first and the third groups, dipslayed that, estimated blood loss was significantly reduced with misoprostol (179 vs 321 mL, p<0.05). Differences were more evident in the size subgroups 5-7 cm, and ≥7 cm [7].

This is also similar to Kalogiannidis et al., who conducted their study on a total of 64 menstruating cases with three or fewer myomas of a maximal diameter of ninety millimeter, planned for myomectomy, being haphazardly assigned to receive a presurgical single dosage of vaginal misoprostol or placebo. They were divided into 30 cases in the misoprostol group and 34 in the control group. The mean blood loss was significantly greater in the control group compared to the misoprostol group (217±7 ml versus 126±41 ml). Misoprostol administration has been accompanied by a drop in blood loss of 91 mL [9].

The pharmacokinetics and bioavailability of misoprostol provide certain benefits concerning its usage in myomectomy. Preoperative vaginal or rectal misoprostol adminstartion increase to a lower value compared the oral or sublingual route. Whereas sublingual administration causes the greatest reported serum values, such peak is followed by a compartively rapid reduction within 105 minutes. In contrast, following its vaginal application, maximum plasma values are much lower, while their reduction is gradual and is sustained to a greater level for up to five to six hours compared to the sublingual administration, in particular when water is utilized to dampen the tablets. In contrast, vasopressin is a rapidly acting strong vasoconstricting agnet, while its actions remain for only thirty five min, which for major approaches and multiple myomectomies makes re-adminstartion important to accomplish continued vasoconstriction [10].

In a prospective RCT conducted by Mohamed et al., on a total of 50 females undergoing myomectomy who were divided into two groups, the control group (group I) consisted of 25 cases receiving two tablets transrectally one hour prior to surgery and no treatment to minimize blood loss. The study group (group II) consisted of 25 cases who received 400μg of misoprostol transrectally one hour prior to surgery. Both groups demonstrated insignificant difference concerning BT [11].

The presnet study demonstarted that there was a significant relationship between number of liomyoma and maximum diameter of fibroid and between HB level, hematocrit level, MCV and MCH pre and post treatment. Our study is the only study directly comparing misoprostol and vasopressin as single agents in myomectomy. To the best of our knwoldege, it's the first research to assess the correlation between number of fibroid and maximum diameter of fibroid and between HB level, hematocrit level, MCV and MCH pre and post treatment.

Mohamed et al., found that there were highly statsiscally significant increases in both postsurgical HB (10.6±0.96 vs. 9.76±0.78) and HCT (33.46±3 vs. 31±2.3) values in the misoprostol group compared to the placebo group (P<0.001) [11].

In the same line, Kalogiannidis et al., displayed that the drop of postsurgical Hb was significantly greater in the placebo group (1.6g/dL ±0.43) in comparison with the misoprostol group (one g/dL±0.3) [9]. In agreement, Shokeir et al., displayed that there was a significant reduction in HB value in the control group (postsurgical 24 hours)

compared to the dinoprostone group [12]. Likewise, Biswas et al., revealed that the postsurgical drop in HB was smaller in the misoprostol group (1.1g/dL) than in the controls (1.9 g/dL) [13]. In contrast, Chai et al., displayed that no significant difference was recorded concerning postsurgical HB concentration between misoprostol and the controls group [14].

CONCLUSION

In the context of myomectomy, vaginal misoprostol could be effective as vasopressin in decreasing blood loss. Since no significant difference was detected between Vasopressin and misoprostol group concerning Intra operative blood loss. Furthermore, no statistically significant relation between number of fibroid and maximum diameter of fibroid and between intraoperative blood loss. A statistically significant decrease in HB level after treatment as compared to pretreatment value, HCT value, MCV & MCH concerning number of fibroid, type of fibroid and maximum diameter of fibroid in both of the studied groups.

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