

The efficacy and safety of preoperative intravenous carbetocin versus rectal misoprostol in reducing blood loss during open myomectomy

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Abstract

AIM: our paper aims to examine the effectiveness and safety of rectal misoprostol and intravenous carbetocin in preventing blood loss during open myomectomy.

Methods: Abdominal myomectomy was performed on 63 female patients who matched the inclusion criteria and had uterine fibroids. With a ratio of 1:1:1 (n=21 in each group), patients were randomly allocated to one of three groups: A for the carbetocin group, B for the misoprostol group, or C for the control group. The three groups were examined with regard to the estimated blood loss (EBL) during open myomectomy, the need for blood transfusion, the length of the procedure, the postoperative hematocrit and hemoglobin, the negative effects of carbetocin and misoprostol, the decline in hemoglobin, and the decline in hematocrit.

Results: There was a highly statistically significant difference between the groups in terms of estimated blood loss (EBL), with carbetocin being superior to the misoprostol and control groups (P-value = 0.024) and the latter being superior to the former (P-value 0.001), respectively. Postoperative hematocrit was also significantly higher in the carbetocin and misoprostol groups compared to the control group (P-value 0.001). Additionally, when assessed 24 hours postoperatively, patients who received carbetocin exhibited a reduced reduction in their hemoglobin and hematocrit levels compared to those who received misoprostol and the control group (P-value = 0.038)(P-value = 0.040). However, there were no statistically significant differences in the three groups' needs for blood transfusions or for misoprostol and carbetocin side effects.

Conclusion: intravenous injection of 100 µg of Carbetocin before skin incision is more effective than rectal misoprostol in decreasing blood loss during abdominal myomectomy and had lower drop in hemoglobin and hematocrit; both carbetocin and misoprostol have more postoperative hematocrit and shorter operative time than control group. While all groups were equal regarding the need for blood transfusion and side effects of carbetocin and misoprostol.

Key words: Carbetocin –misoprostol – myomectomy –hemostasis

Introduction

Women frequently have pelvic tumors called uterine leiomyomas. Symptoms such as abnormal uterine hemorrhage and/or pelvic pain/pressure are often present. Fibroids develop in people who are of reproductive age and may also have implications on reproduction, such as infertility or unfavorable pregnancy outcomes [1].

Treatment options for fibroid-related symptoms include managing symptoms during pregnancy, medical therapy, non-excisional procedures (endometrial ablation, uterine artery embolization, magnetic resonance guided focused ultrasound), and surgery (myomectomy, radiofrequency ablation, hysterectomy).[2]. The standard course of care for people who don't want to get pregnant is hysterectomy. Patients who want to protect their fertility in the future or who reject hysterectomy often seek myomectomy. Early in the 20th century, abdominal myomectomy, also known as open myomectomy, was created as a conservative therapy for women with uterine myomas[3].

Myomectomy may result in higher blood loss because uteri with myomas have a greater blood supply. 200 to 800 ml of blood on average are lost during abdominal myomectomy, and 80 to 250 ml with laparoscopic myomectomy. Anemia, unstable coagulation, and hypervolemia may all be side effects of surgical hemorrhage[4]. Mechanical or pharmaceutical techniques may be used to stop bleeding or lessen its severity[5].

The mechanical tourniquet has been used during myomectomy to prevent intraoperative bleeding, and uterine artery closure may limit both intraoperative and postoperative hemorrhage[6]. Hormonal tourniquets like terlipressin and vasopressin, which reduce blood loss, target the myometrium-expressed vasopressin V1 receptor[7]. Preoperative uterine artery embolization reduces uterine size, controls symptoms, and may be a successful therapy for people with large fibroids[8]. Laparoscopic bipolar coagulation and laparoscopic dissection of the uterine blood arteries have also been considered as alternatives to uterine artery embolization[9]. Among other uterotonics, misoprostol and ergometrine cause myometrial contraction, which lessens blood loss during myomectomy and enhances uterine structural reconstruction[10].

Carbetocin is a synthetic version of oxytocin with a 40-minute half-life and 80% bioavailability. Within less than two minutes of giving this medicine intramuscularly or intravenously, uterine contractions start. The uterine response to carbetocin lasts longer than the uterine response to oxytocin in terms of frequency

and amplitude of contractions. According to recent studies, carbetocin may reduce blood loss during myomectomy [11]. This research compares the effectiveness and safety of rectal misoprostol with intravenous carbetocin in preventing blood loss during open myomectomy.

Patients and methods

The Obstetrics and Gynecology Department at Cairo University performed this investigation, which was a prospective randomized controlled clinical trial, over a period of time. from July 2019 to March 2021.

Study Population:

Women attending Obstetrics and Gynecology department planning for myomectomy were recruited. This study was conducted on three groups:

1. Group A: 21 women (carbetocin group).
2. Group B: 21 women (misoprostol group).
3. Group C: 21 women (control group)

Ethical Considerations:

The ethics committee of the department of obstetrics and gynecology, college of medicine, Cairo University, gave its clearance before this research could be carried out. All participants gave their informed permission before being included in the research and after being informed of its goals and methods.

Inclusion and exclusion criteria:

We included in our study ; Number of myoma ≤ 5 , Size >3 cm and staging of myoma from (1 to 6) according to FIGO staging :

submucous $<50\%$ intramural, submucous $\geq 50\%$ intramural, contacts endometrial 100% intramural, intramural (not contacts endometrial), sub serosal $\geq 50\%$ intramural and sub serosal $<50\%$ intramural

we excluded patients received preoperative embolization of uterine artery or GnRh analogue, anemia (defined as a hematocrit of less than 36 percent in women) and Bleeding tendency related to medical disorder (valve replacement on Marivan or coagulopathy).

Allocation and randomization:

Group assignment: On the day of surgery, patients were divided into three parallel groups using a computer-generated randomization procedure, with the groups coded A, B, and C (A for carbetocin group, B for misoprostol group, and C for control group) at a 1:1:1 ratio.

Study Techniques:

Prior to the procedure, participants were divided into one of three groups:

Prior to making the skin incision, Group A got 100 g of carbetocin (1 ml) slowly administered intravenously in 5 ml of saline.

Group B got two pills containing 400 mcg of misoprostol transrectally one hour prior to surgery.

Group C: No medicine was administered prior to skin incision

Anesthesia: General anesthesia was commonly used to accomplish abdominal myomectomy.

Procedure: A laparotomy, or transverse incision (such as the Pfannenstiel), was used to execute an abdominal myomectomy.

the use of measures to limit blood loss, the correction of preoperative anemia, Additionally, we plan for the use of blood transfusions for women in whom we expect severe blood loss (300 ml). If vital signs (pulse >100 bpm, systolic blood pressure 100 mmHg, and urine output 45 ml/h) worsened during surgery, transfusion was initiated.

B. Uterine incision; an opening in the uterus that allows for the removal of all or the majority of the myomas.

C. Remove myomas: The uterine incision was made all the way through the fibroid pseudocapsule and myometrium. Once the myoma has been identified, this incision may be extended a little bit deeper than the capsule to access the least vascular plane. The myoma might then be seen clearly and may even swell somewhat.

D. Repair uterine defects. If the myometrial defect was deep (more than 2 cm), two layers of sutures were required to reapply the tissue and establish hemostasis.

E. The formula used to determine Estimated Blood Loss (EBL) was as follows:

Preoperative and postoperative hematocrits are expressed as $EBL = EBV$, respectively.

where EBV (weight in kg divided by 70) is the patient's expected blood volume in milliliters. (Gross, 1983)

F. After myomectomy, all patients were observed for the following things: the need for blood transfusions (within the first 24 hours), postoperative hematocrit after 24 hours, side effects of misoprostol (within the first 6 hours) (such as shivering, pyrexia $>38^{\circ}\text{C}$, diarrhea, nausea, and vomiting), and side effects related to carbetocin (such as hot flush, nausea, and back pain).

Outcomes:

primary results

to compare the three groups' estimated blood losses (EBL) after open myomectomy.

secondary outcome metrics; blood transfusion need, the length of the operation, the post-operative hematocrit, the post-operative hemoglobin, Hematocrit and hemoglobin levels dropping, as well as misoprostol and carbetocin side effects.

Statistical analysis

The statistical program for the social sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) was used to code and input the data. For quantitative variables, mean and standard deviation were used to describe the data, and for categorical variables, frequencies (the number of instances) and relative frequencies (percentages) were used. For comparisons between groups, analysis of variance (ANOVA) with multiple comparisons post hoc test was used for quantitative variables with regularly distributed distribution, while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for quantitative variables with non-normally distributed distribution. Using the Chi square (χ^2) test, categorical data were compared. When the anticipated frequency was less than 5, the Fisher Exact test was employed instead. P-values under 0.05 were regarded as statistically significant.

Result

	carbetocin	Misoprostol	Control	p-value
Age	30.05 +6.66	29.95 +4.92	31.29 +5.39	0.701
Weight	74.29 +9.31	73.67 +10.06	73.90 +12.26	0.982

EBV	5200.00 +651.47	5156.67 +704.30	5173.33 +858.44	0.982
Number of myomas	2.43 +0.93	2.33 +1.02	2.52 +0.93	0.793

There were no statistically significant differences regarding age, weight, estimated blood volume, number of myomas between groups.

	carbetocin	Misoprostol	Control	p-value
PreHCT	40.02+2.31	40.09 + 2.70	39.96 + 3.00	0.987
postHCT	37.94 +2.60	36.76 + 2.51	33.87 + 3.25	<0.001
MeanHCT	38.98 +2.42	38.43 +2.50	38.58 + 7.80	0.933
PreHB	13.30 +0.80	13.26 +0.89	13.32 +1.01	0.975
PostHB	12.61+ 0.91	12.17 +0.92	11.33 +1.15	<0.001
operativetime	69.05 +9.57	73.57 +6.55	82.14 +6.99	<0.001

There were no statistically significant differences regarding preoperative hematocrit (HCT), preoperative hemoglobin (HB), and mean hematocrit between the three groups. On other hand there were statistically significant differences regarding post-operative hematocrit (P-value > 0.001), postoperative hemoglobin (P-value > 0.001) and operative time (P-value > 0.001).

		carbetocingroup	misoprostolgroup	controlgroup
postHCT	carbetocingroup		0.538	<0.001
	misoprostolgroup	0.538		0.004
	controlgroup	<0.001	0.004	
operativetime/min	carbetocingroup		0.197	<0.001
	misoprostolgroup	0.197		0.002
	controlgroup	<0.001	0.002	
PostHB	carbetocingroup		0.458	<0.001
	misoprostolgroup	0.458		0.027
	controlgroup	<0.001	0.027	

Regarding postoperative HCT, there were no statistically significant differences between the carbetocin and misoprostol groups, but there were statistically significant differences between the two and the control group (P-values > 0.001, respectively; P-value = 0.004). Regarding operating time, there were no statistically significant differences between the carbetocin and misoprostol groups, but there were (P-value > 0.001) and (P-value = 0.002), respectively, statistically significant disparities between the two groups and the control group. Regarding

postoperative HB, there were no statistically significant differences between the carbetocin and misoprostol groups, however there were (P-value > 0.001) and (P-value = 0.027) between the two groups and the control group.

	carbetocin	Misoprostol	Control	p-value
Ch in HCT	2.08+0.84	3.33+1.48	6.09+2.17	<0.001
EBL	282.37+133.77	449.77+209.96	849.17+355.20	<0.001
Chin HB	0.69+0.27	1.10+0.46	1.99+0.74	<0.001

There were statistically significant differences regarding estimated blood loss, drop in hematocrit and hemoglobin between the three groups (P- value > 0.001).

		P-value
Ch in HCT	carbetocin group VS misoprostol group	0.040
	carbetocin group VS control group	< 0.001
	misoprostol group VS control group	0.003
Estimated blood loss	carbetocin group VS misoprostol group	0.024
	carbetocin group VS control group	< 0.001
	misoprostol group VS control group	0.005
Chin HB	carbetocin group VS misoprostol group	0.038
	carbetocin group VS control group	< 0.001
	misoprostol group VS control group	0.003

Between the carbetocin and misoprostol groups, the drop in hematocrit showed statistically significant differences (P-value = 0.040), as did the differences between the carbetocin and control groups (P-value > 0.001), as did the differences between the misoprostol group and the control group (P-value = 0.003). In terms of estimated blood loss, there were statistically significant differences between the carbetocin and misoprostol groups (P-value = 0.024), as well as between the carbetocin and control groups (P-value > 0.001), and between the misoprostol group and the control group (P-value = 0.005). In terms of hemoglobin drop, there were statistically significant differences between the carbetocin and misoprostol groups (P-value = 0.038), as well as between the carbetocin and control groups (P-value > 0.001), and between the misoprostol group and the control group (P-value = 0.003).

	carbetocin	Misoprostol	Control	p-value
Needforblood	0	1 (4.8%)	4 (19.0%)	0.116
Shivering	0	2 (9.5%)	0	

&Pyrexia				0.323
Hotflush	2 (9.5%)	1 (4.8%)	0	0.767
Nausea	21 (100.0%)	21 (100.0%)	21 (100.0%)	-----
Vomiting	1 (4.8%)	0	0	1
Diarrhea	0	1 (4.8%)	0	1
Abdominal pain	0	2 (9.5%)	0	0.323

There were no statistically significant differences in the number of patients who required blood transfusions, however the number of patients in the control group (n=4) compared to the carbetocin (n=0) and misoprostol (n=1) groups was greater. Although there were no statistically significant differences between carbetocin and misoprostol in terms of side effects, the incidence of hot flush (n=2), shivering (n=2), diarrhea (n=1), and stomach discomfort (n=2) were greater in the carbetocin group.

Discussion

Hemorrhage is the main risk with open myomectomy. The number and size of the fibroids excised as well as the method used during the myomectomy are major determinants of intraoperative bleeding[12]. There are several methods available to reduce intraoperative bleeding, however comparing their effectiveness may be challenging because to variations in patient characteristics. As a result, there is still no consensus about the ideal hemostasis technique[13].

The current analysis agreed with the randomized comparative study by Elfeky et al. (2020). After undergoing abdominal myomectomy, sixty female patients were randomly divided into two groups. Group (I): A 30-patient female intramural carbetocin group. 30 female patients participated in group (II) (rectal misoprostol group). The findings corroborated earlier study by Fang (2009)[14] that demonstrated intra-myometrial carbetocin injection during abdominal myomectomy surgery is more effective in reducing blood loss than rectal misoprostol. He divided 54 myomectomy patients into two groups for his study. Patients in the first group were given a 100 g injection of carbetocin after their myomectomy, whereas those in the second group were given a 20 u injection of oxytocin. Variations in adverse effects, uterine contraction, and average bleeding quantity were found. There was less bleeding in the first group, and the uterine

contraction in the first group was greater than the one in the second group. Carbetocin may promote uterine contraction and reduce bleeding during the myomectomy.

According to a separate randomized controlled experiment conducted by Gad Allah et al. (2015)[14], this was done. 20 patients from each of two groups of women who were scheduled for myomectomy participated in that research. In the control group, hemostasis was achieved using tourniquets on the uterine arteries. However, in the study group, carbetocin injections into the myometrium immediately resulted in hemostasis. Because of the intra-myometrial Carbetocin injection, less blood was lost during the myomectomy. Patients who took carbetocin showed less of a decline in their hemoglobin and hematocrit levels when checked 48 hours following surgery.

Our results are supported by Yang et al.'s (2012)[15] study, whose major objective was to evaluate the efficacy and safety of carbetocin administration to reduce bleeding during laparoscopic myomectomy. Retrospective review of 70 patients' clinical records was done. The 70 patients were divided into two groups: one got preoperative carbetocin as therapy, the other preoperative oxytocin administered similarly to the treatment group. The following were noted: blood loss, operating time, postoperative hemoglobin (Hb) levels, and postoperative hospital stay. The outcomes showed that there was a substantial difference between the treatment and control groups in terms of blood loss, operating time, HB value, and hospital stay. Without switching to open surgery, all patient had successful procedures.

According to another research, Celik and Sapmaz (2003) performed an abdominal myomectomy on 25 women with symptomatic uterine fibroids in a placebo-controlled randomized prospective trial. One hour before to the surgery, individuals in the experimental group (n = 13) got a single dosage of vaginal misoprostol (400 g), whereas those in the control group (n = 12) received a placebo. Between the two groups, comparisons were made regarding the quantity of intraoperative blood loss, the duration of the surgery, the length of the postoperative hospital stay, and the need for blood transfusion. Depending on the amount of blood lost, different patients' hospital stays varied in length[6].

Elhoussieny et al.'s (2020)[16] randomized controlled study, which included 44 women, revealed the opposite; it revealed that group 1's 22 patients got 400 ug of misoprostol vaginally an hour before to surgery. The study discovered no statistically significant variations in the expected blood loss between the women in

the two groups (P=0.730). The 22 patients in Group 2 would slowly receive an intravenous bolus of 100 µg carbetocin.

Elhoussieny et al. (2020) agreed that while there was no statistically significant difference in post-operative hematocrit and post-operative hemoglobin between group A and group b, both groups had significantly higher levels than group c.[16] Postoperative Hb and postoperative HCT did not differ substantially between women in either research group when study groups were compared. In their study, Gad Allah et al. (2015)[14] also found a significant decrease in postoperative HB in the control group (P 0.05). Contrarily, Sallam and Shady's (2018) results showed that while the study group's hemoglobin levels were lower, they did not reach statistical significance (P=0.069) when comparing pre- and post-operative hemoglobin levels and identifying the change in hemoglobin.

Conclusion: This study demonstrated that, while both drugs are equally safe for women, preoperative intravenous injection of 100 mg carbetocin is more effective than rectal misoprostol 400 mg in reducing blood loss during myomectomy and shows less drop in hemoglobin and hematocrit when measured 24 hours postoperatively.

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