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Effectiveness of intravenous carbetocin in reducing blood loss during abdominal myomectomy, a clinical trial

IV carbetocin during abdominal myomectomy.

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ABSTRACT

Objective. Myomectomy is advised for symptomatic uterine leiomyomas in women who wish to preserve fertility and is associated with major blood loss. The study aims to assess the effectiveness of intravenous Carbetocin to control blood loss during abdominal myomectomy compared to pre-operative vaginal Misoprostol, intraoperative Oxytocin infusion, and using pericervical tourniquet.

Materials and Methods. This clinical trial included 120 women candidates for abdominal myomectomy and was randomized into four groups (30 in each). Group 1 received pre-operative vaginal Misoprostol. Group 2 started and continued an infusion of Oxytocin during myomectomy. Group 3 received Carbetocin just before the skin incision. Group 4 had a pericervical tourniquet during the myomectomy.

Results. In the Carbetocin group, the intraoperative blood loss was the least (285.50±33.12 ml) compared to the Misoprostol group (439.33±40.23 ml), the Tourniquet group (497.33±29.35 ml), and the Oxytocin group (607±44.81 ml). The hemoglobin and hematocrit reduction were the least in the Carbetocin group (0.71±0.17 gm/dl and 1.09±0.34%) compared to the Misoprostol group (1.16±0.43 gm/dl and 2.7±1.21%), the Tourniquet group (1.85±0.3 gm/dl and 2.87±0.92%), and the Oxytocin group (1.95±0.32 gm/dl and 3.39±1.76%). The operative time and the postoperative hospital stay were the least in the Carbetocin group (58±6.43 min / 1.23±0.43 days) compared to the Misoprostol group (75.73±4.62 min / 1.67±0.55 days), the Tourniquet group (80.87±3.43 min /1.97±0.41 days), and the Oxytocin group (88.1±4.62 min / 2.2±0.48 days).

Conclusions. Carbetocin during abdominal myomectomy is the most effective method as regards blood loss, operative time, postoperative hemoglobin and hematocrit, and postoperative hospital stays.

Key words

Myomectomy; misoprostol; oxytocin; carbetocin; tourniquet.

Introduction

Different modalities have been introduced for treating symptomatic uterine leiomyomas in women who wish to preserve their fertility, including medical treatment, myomectomy, and uterine artery embolization [1,2]. Myomectomy can be performed by laparotomy, laparoscopy, or hysteroscopy (transvaginal) procedures. Many factors may influence the choice of surgical route for myomectomy, such as the position, size, and number of uterine myomas, the presence of other coexisting pelvic diseases, the surgeon's expertise, surgical competence, and prejudice, as well as the availability of suitable equipment [3].

Myomectomy may be associated with major blood loss, especially abdominal myomectomy. The average blood loss after an open abdominal myomectomy varies in different reports, ranging between 370 and 840 mL. Blood transfusion rates ranged from 21% to 50% in over 175 open abdominal myomectomy procedures. The increased size and number of myomas and their proximity to the uterine cavity correspond to higher blood loss [4].

Several techniques have been developed to minimize the possible blood loss, including (a) the dissection technique (vertical, anterior uterine incision) or the use of laser, electrosurgery, and chemical dissectors, (b) mechanical procedures on the uterine and/or ovarian arteries, such as pre-operative uterine/ovarian embolization or clamping, or intraoperative pericervical mechanical tourniquet, (c) medical agents including medical uterotonics (Oxytocin, Carbetocin, Misoprostol), a hormonal tourniquet (intraoperative vasopressin or terlipressin injection), or intramyometrial injection with bupivacaine plus epinephrine, and (d) GnRH analogues 2–4 months preoperatively [5–11]. However, vasopressin may cause pulmonary edema, myocardial infarction, and a transient rise in blood pressure [12]. In addition, GnRH analogues are costly, and patients may face side effects of estrogen deficiency when given without hormone replacement therapy [13].

Despite the number of studies on methods to achieve good hemostasis during the open myomectomy, there is still not enough data from well-designed comparative randomized controlled trials. As a result, discrepancies in patient variables (age and ethnicity) and fibroid characteristics (size, location, and number) make it impossible to compare the currently known randomized studies. Therefore, there is still no agreement on the optimal approach [14].

Objectives

This study aims to study the effectiveness of intravenous Carbetocin intraoperatively in controlling blood loss during abdominal myomectomy compared to pre-operative dose of vaginal Misoprostol, intraoperative Oxytocin infusion, and pericervical tourniquet.

Materials and Methods

Study registration, ethical and methodological standards

The research protocol was approved by the Research Ethics Committee on the date and number of approvals. The study was registered at the ClinicalTrials.gov registry with a registration number of NCT04595812.

Patient and public involvement

This clinical trial was conducted on 120 women with symptomatic uterine fibroid who were candidates for abdominal myomectomy and presented to Cairo University outpatient gynecological clinic.

The eligibility criteria included women candidates for abdominal myomectomy aged between 20-40 years, BMI less than 30 kg/m^2, 1-5 myomas by ultrasound (intramural, submucous, subserous), size of the uterine myomas ranging from 5-10 cm, and symptomatic with abnormal uterine bleeding, pain, abdominal enlargement, infertility, or recurrent miscarriage.

The exclusion criteria were (1) pregnant or postmenopausal women, (2) patients with pedunculated subserous fibroid, (3) patients who were candidates for laparoscopic or hysteroscopic myomectomy, (4) history of previous abdominal or pelvic surgery except for Cesarian section, (5) history of pelvic or ovarian endometriosis or PID, (6) allergy to Misoprostol, (7) medical disorders such as hypertension, diabetes mellitus, cardiac and pulmonary diseases, (8) anemia with Hb < 10 g/dL, (9) bleeding disorder or use of anticoagulation, and (10) pre-operative use of hormonal therapy as GnRH analogues or oral contraceptive pills.

All 120 patients were subjected to history taking (gynecological, medical, and surgical history) and comprehensive general and pelvic examination. They also underwent the following investigations: CBC, coagulation profile, blood group, and ultrasound scan for detection of the size, number, and location of myoma.

After signing an informed written consent for the surgery and recruitment in the study, patients were randomized to one of four groups (30 in each group) by using a computer software (Microsoft Excel), using a randomization pattern of 1:1:1:1. Randomization cards created by computers were stored in opaque, sealed envelopes with sequential numbers. To perform block randomization, each group's management protocol was written and sealed in an envelope with a computer-generated number. Participants were identifiable by their randomization numbers until they were discharged from the hospital.

Data collection

The patients were randomized into one of four groups as follows:

1. Group 1 (Misoprostol group): they received two tablets of 200 µg Misoprostol (Cytotec, Pfizer Limited, United Kingdom) administered into the posterior fornix of the vagina 1 hour before the onset of surgery.
2. Group 2 (Oxytocin group): After induction of general anesthesia and immediately prior to the operation, an infusion of 30 IU Oxytocin in 500 ml normal saline at a rate of 120 ml/h was started and continued during myomectomy.
3. Group 3 (Carbetocin Group): they received 100 µg IV Carbetocin (1 ml) [Pabal, Ferring (UK)] in 5 ml saline over 1 minute just before skin incision.
4. Group 4 (pericervical tourniquet Group): The broad ligament was examined and felt slightly above the internal cervical os to locate an area devoid of blood vessels and the ureter. Following that, a 1-cm incision was performed bilaterally in this clean area. A Foley catheter size 18 was inserted via the incisions, the ends protruding anteriorly, drawn tight, and secured with a Kelley clamp. The time it took to apply the tourniquet was documented and

removed no later than 45 minutes later. The tourniquet was reinserted after at least 15 minutes for individuals who needed more than one application.

A surgical team of the same consultants utilized a standard technique to conduct abdominal myomectomy using the same procedure on all the patients. All surgeons attempted to remove fibroids with minimal incisions made either anteriorly or posteriorly. The size and number of myomas in all patients were measured after they were removed.

Intraoperative blood loss was estimated by calculating the sum of canisters (irrigation fluids and suctioned blood) minus the used irrigation solution plus the amount of absorbed blood in used sponges, which was obtained by subtracting the pre-operative dry sponge weight (grams) from the postoperative wet sponge weight in (grams), then converting weight into a volume of blood loss (1 gm means 1 ml of blood weighs).

Hemoglobin (Hb) and hematocrit (Hct) levels were evaluated 24 hours before and after the operation. Full postoperative observational records were completed, including pulse, blood pressure, temperature, fluid intake, urine output, and the requirement for a blood transfusion. The need for blood transfusion was decided according to standard guidelines, such as the estimated volume of blood loss, Hb level, and clinical signs, such as blood pressure and heart rate. Linen towels used for myomectomy were weighed before and after the procedure. The difference in weight between the soaked and dry linen towels was determined.

Sample Size:

In a previous investigation, the blood loss difference between intramyometrial Carbetocin injection and control during myomectomy was 149±203 ml. Using the power of 80% and 5% significance level, 30 patients were required in each group (120 total). The sample size was calculated using "Power and Sample Size Calculation Software" v.3.1.2 (Vanderbilt University, Nashville, Tennessee, USA).

Statistical analysis

Data were revised and stored using computer software "Microsoft Excel 2019", then data was transferred to advanced statistics software "Statistical Package of Social Science" (SPSS v.26) to be statistically analyzed. Quantitative variables were described as mean, standard deviation, median, and range, then were compared using the ANOVA test. Qualitative variables were described as frequency and percentages, then were compared using Chi-square or Fisher exact test as appropriate. The P-value was considered significant if less than 0.05.

Results

Following the CONSORT guidelines, 120 women were included **(Figure 1)**. As shown in **Table 1**, there was no significant difference between groups in the demographic criteria regarding age (P=0.795), BMI (P=0.895), gravidity (P=0.523), parity (P=0.802), and history of previous Cesarian section (P=0.962). As regards pre-operative investigations, there was no significant difference between groups regarding the number of myomas (P=0.934), size of largest myoma (P=0.266), type of myoma regarding its site (P=0.958), pre-operative Hb (P=0.755), and pre-operative Hct (P=0.675).

Table 2 showed significant differences between groups regarding intraoperative blood loss, the total estimated blood loss, operation time, postoperative Hb and Hct, drop in Hb and Hct, and

postoperative hospital stays. Therefore, we did a second analysis (Tukey HSD post-hok test) to detect the significance between every two groups separately in **Tables 3** and **4**. There was no statistically significant difference between the four groups regarding the need for blood transfusion.

The Carbetocin group had the least intraoperative blood loss (285.50±33.12 ml) compared to the Misoprostol, Tourniquet, and Oxytocin groups. The total estimated blood loss was also the least in the Carbetocin group (292.17±45.97 ml) compared to the Misoprostol, Tourniquet, and Oxytocin groups.

The reduction in Hb and Hct was the least in the Carbetocin group (0.71±0.17 gm/dl and 1.09±0.34%) compared to the Misoprostol, Tourniquet and Oxytocin groups. Therefore, the postoperative Hb and Hct were highest in the Carbetocin group (10.49±0.56 gm/dl and 33.27±1.88%) compared to the Misoprostol, Tourniquet and Oxytocin groups.

The operative time was the least in the Carbetocin group (58±6.43 min) compared to the Misoprostol, Tourniquet, and Oxytocin groups. The postoperative hospital stay was also the least in the Carbetocin group (1.23±0.43 days) compared to the Misoprostol, Tourniquet, and Oxytocin groups.

Discussion

Main findings

Myomectomy is a conservative surgery aiming to treat symptomatic uterine fibroids while preserving fertility. The most significant surgical complication is uncontrolled intraoperative bleeding, which puts the procedure at even greater risk than a hysterectomy. It also necessitates the expertise of a qualified surgeon and increases the risk of postoperative anemia, intraoperative hypovolemic shock, infertility related to adhesions, and pelvic infections. A recent study reported that 81% of patients who had open myomectomy without measures to control blood loss had blood loss of 500 - 1000 ml and 16% more than 1000 ml of blood [15].

Many studies have been conducted to evaluate the effectiveness of different approaches to reduce bleeding during myomectomy, including the use of uterotonics (Misoprostol, Ergometrine, Oxytocin, and Carbetocin), hormonal tourniquet (vasopressin), and mechanical methods (peri-cervical tourniquet) [4–10]. However, variations in patient characteristics make it impossible to compare effectiveness. As a result, there is no consensus on the preferred approach to reduce intraoperative blood loss [14].

oxytocin analog with a significantly longer half-life than endogenous or synthetic oxytocin.

Carbetocin is a synthetic oxytocin analogue that acts similarly to oxytocin in the myometrium by binding to oxytocin receptors and inducing uterine contractions via the same mechanism. Its half-life is noticeably longer than that of synthetic or endogenous oxytocin [16]. Our study found that intravenous injection of Carbetocin during abdominal myomectomy is the most effective method to reduce intraoperative blood loss, total estimated blood loss, operative time, reduction in Hb and Hct, and postoperative hospital stay.

Strengths and Limitations

Points of strength in our study include that it is a randomized controlled study and that we compared different methods to control blood loss during abdominal myomectomy. In our study, intraoperative blood loss was found to be the least with Carbetocin. This could be attributed to the fact that Carbetocin makes a longer uterine response in terms of the frequency and amplitude of

contractions [17]. Points of weakness in our study include the small number of patients and the cost of Carbetocin (the most expensive of all methods used).

Interpretation and comparison with other literature

In comparison with using pre-operative vaginal Misoprostol, our results showed that intraoperative and total blood loss in the Carbetocin group was statistically less than in the Misoprostol group. Postoperative Hb and Hct values were also statistically higher in the Carbetocin group than in the Misoprostol group. In addition, the operative time and the postoperative hospital stays were statistically less in the Carbetocin group than in the Misoprostol group. This could be explained by shorter placental separation time as well as strong contraction caused by carbetocin, which means that less uterine massage is required during the procedure, allowing the surgeon to focus more during surgery [18,19].

Similar results were found by Elfeky et al. (2020), who studied sixty patients undergoing abdominal myomectomy and randomly assigned them into two equal groups. In the Carbetocin group, 100 µg Carbetocin diluted within 10 ml saline (0.9%) was injected intramyometrium in the planned uterine incision site for fibroid extraction just before the incision. On the other hand, two tablets (400 mcg) were administered rectally one hour before the abdominal myomectomy operation in the Misoprostol group. The blood loss in the Carbetocin group was considerably less than in the Misoprostol group (542 ± 49.72 ml vs 574 + 63.87 ml, P=0.034) [20].

They also found that postoperative Hb and Hct values were considerably higher in the Carbetocin group (9.99± 1.15 gm/dl and 30.99±1.22) than the Misoprostol group (9.02± 1.10 gm/dl and 30.14±0.94) with a p-value of 0.002. In addition, they found that the operative time in the Carbetocin group (91.67±9.65 min) was less than that in the Misoprostol group (94.67±11.99 min) but with no statistically significant difference (p=0.290). They also found that the hospital stay in the Carbetocin group (3.53± 0.43 days) was less than that in the Misoprostol group (3.62± 0.36 days) but with no statistically significant difference (p=0.424).

Compared to using a pericervical tourniquet, our results showed that intraoperative and total blood loss in the Carbetocin group were considerably less than in the Tourniquet group. The drop in Hb and Hct values was also considerably lower in the Carbetocin group than in the Tourniquet group. In addition, the operative time and the postoperative hospital stays were considerably less in the Carbetocin group than in the Tourniquet group.

On the contrary, a randomized controlled trial was conducted by Gamal et al. (2023) at Ain Shams University Maternity Hospital, in which 111 women scheduled for open myomectomy were placed into two groups of 55 patients each. Hemostasis was achieved in the control group using the uterine artery Tourniquet method, but the study group had intraoperative 100 ug of IV Carbetocin. They found no statistically significant difference between both groups regarding blood loss [21].

Compared with the Oxytocin group, our results showed that intraoperative and total blood loss in the Carbetocin group was considerably less than in the Oxytocin group. The reduction in Hb and Hct values was also considerably lower in the Carbetocin group than in the Oxytocin group. In addition, the operative time and the postoperative hospital stays were considerably less in the Carbetocin group than in the Oxytocin group.

Ahmed et al. (2021) compared 100 pregnant women, of whom 50 received Carbetocin vs 50 received Oxytocin. The average blood loss in the Carbetocin group was considerably less than that of the Oxytocin group (732 [IQR 232] vs 910 [IQR 318], P=0.004). The mean reduction of Hb in the Carbetocin group was considerably less than that of the Oxytocin group, with a P-value <0.001. The mean reduction of Hct in the Carbetocin group was considerably less than that of the Oxytocin group, with a P-value of 0.019. [22].

Conclusions

During abdominal myomectomy, intraoperative use of Carbetocin injection achieved the least blood loss, highest postoperative Hb and Hct levels, least operative time and postoperative hospital stay, and the least need for blood transfusion compared to transvaginal Misoprostol, intravenous Oxytocin, and pericervical tourniquet.

Compliance with Ethical Standards

Authors contribution: AA, SA, MR designed and supervised the study. RE, AS conducted the study and analyzed the data. MA analyzed the data. All authors wrote the draft manuscript and approved the final manuscript.

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Study registration: The trial was registered in ClinicalTrials.gov registry, with number NCT04595812. https://clinicaltrials.gov/study/NCT04595812.

Disclosure of Interests: None of the authors has financial or other conflicts of interest.

Ethical Approval: The study protocol was approved by the Research Ethics Committee with reference number (MD-301-2020). All methods were carried out in accordance with relevant guidelines and regulations.

Informed consent: All participants gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

Data sharing: The data that support the findings of this study are available from Kasr El-Ainy Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Kasr El-Ainy Hospital.

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Table 1: Patients' characteristics and pre-operative investigations

	Misoprostol Group (n=30)	Oxytocin Group (n=30)	Carbetocin Group (n=30)	Tourniquet Group (n=30)	P-value
Age (years)	31.03 ± 6.29 31.5 (20 - 40)	31.43 ± 5.35 30.5 (20 - 40)	32.33 ± 6.05 33.5 (21 - 40)	31.00 ± 5.51 31 (20 - 40)	0.795
BMI (kg/m²)	23.23 ± 2.88 23.5 (18 - 28)	22.97 ± 2.57 23 (18 - 28)	22.70 ± 2.78 22.5 (18 - 28)	22.90 ± 2.48 23 (18 - 27)	0.895
Gravidity - NG - G1 - G2 - G3 - G4	 1 (3.33%) 7 (23.33%) 13 (43.33%) 9 (30.0%) 0 (0.0%)	 2 (6.67%) 6 (20.0%) 14 (46.67%) 7 (23.33%) 1 (3.33%)	 3 (10.0%) 3 (10.0%) 9 (30.0%) 12 (40.0%) 3 (10.0%)	 1 (3.33%) 9 (30.0%) 11 (36.67%) 7 (23.33%) 2 (6.67%)	0.523
Parity - P0 - P1 - P2 - P3 - P4	 4 (13.33%) 10 (33.33%) 12 (40.0%) 4 (13.33%) 0 (0.0%)	 3 (10.0%) 12 (40.0%) 12 (40.0%) 3 (10.0%) 0 (0.0%)	 5 (16.67%) 8 (26.67%) 9 (30.0%) 6 (20.0%) 2 (6.67%)	 4 (13.33%) 11 (36.67%) 11 (36.67%) 4 (13.33%) 0 (0.0%)	0.802
Previous CS	11 (36.7%)	12 (40.0%)	11 (36.7%)	10 (33.3%)	0.962
Number of myomas	2.57 ± 1.10 2.5 (1 - 5)	2.43 ± 1.19 2 (1 - 5)	2.60 ± 1.10 2 (1 - 5)	2.60 ± 1.19 2.5 (1 - 5)	0.934
Size of largest myoma	5.87 ± 1.31 5 (5 - 10)	5.97 ± 1.35 5 (5 - 10)	6.53 ± 1.57 6 (5 - 10)	6.00 ± 1.44 5 (5 - 10)	0.266
Types of myoma: - Submucous - Intramural-submucous - Intramural - Intramural-subserous - Subserous	 1 (3.33%) 1 (3.33%) 24 (80.0%) 2 (6.67%) 2 (6.67%)	 1 (3.33%) 1 (3.33%) 25 (83.33%) 2 (6.67%) 1 (3.33%)	 0 (0.0%) 2 (6.67%) 23 (76.67%) 4 (13.33%) 1 (3.33%)	 1 (3.33%) 0 (0.0%) 26 (86.67%) 2 (6.67%) 1 (3.33%)	0.958
Pre-operative hemoglobin (gm/dl)	11.12 ± 0.52 11.05 (10 - 12)	11.15 ± 0.53 11.15 (10 - 12)	11.20 ± 0.51 11.2 (10.3 - 12)	11.06 ± 0.45 11 (10 - 12)	0.755
Pre-operative Hematocrit (%)	34.57 ± 1.81 34 (32 - 39)	34.47 ± 2.06 34 (32 - 39)	34.37 ± 1.83 34 (32 - 38)	34.03 ± 1.30 34 (32 - 38)	0.675

Table 2: Operative and postoperative outcomes in all groups

	Misoprostol Group (n=30)	Oxytocin Group (n=30)	Carbetocin Group (n=30)	Tourniquet Group (n=30)	P-value
Intraoperative blood loss (ml)	439.33 ± 40.23 425 (400 - 600)	607.00 ± 44.81 600 (550 - 700)	285.50 ± 33.12 280 (250 - 350)	497.33 ± 29.35 495 (450 - 550)	**<0.001**
Blood amount in the intraperitoneal drain (ml)	25.00 ± 65.32 0 (0 - 300)	53.33 ± 105.81 0 (0 - 350)	6.67 ± 21.71 0 (0 - 100)	33.33 ± 87.43 0 (0 - 350)	0.132
Total estimated blood loss (ml)	464.33 ± 98.56 435 (400 - 900)	660.33 ± 143.3 600 (550-1050)	292.17 ± 45.97 280 (250 - 420)	530.7 ± 106.35 495 (450 - 900)	**<0.001**
Operation time (min)	75.73 ± 4.62 75 (70 - 88)	88.10 ± 4.62 88 (80 - 95)	58.00 ± 6.43 60 (45 - 66)	80.87 ± 3.43 80.5 (75 - 85)	**<0.001**
Postoperative hemoglobin (gm/dl)	9.96 ± 0.77 10.1 (7 - 11.2)	9.20 ± 0.64 9.25 (7.5 - 10)	10.49 ± 0.56 10.5 (9.6 -11.5)	9.20 ± 0.63 9.25 (7.2 - 10)	**<0.001**
Hemoglobin reduction (gm/dl)	1.16 ± 0.43 1.05 (0.8 - 3)	1.95 ± 0.32 2 (1.5 - 2.5)	0.71 ± 0.17 0.7 (0.5 - 1)	1.85 ± 0.30 1.8 (1.5 - 3)	**<0.001**
Postoperative Hematocrit (%)	31.87 ± 1.40 32 (29 - 35)	31.08 ± 0.84 31 (29 - 33)	33.27 ± 1.88 33 (31 - 37)	31.17 ± 0.72 31.25 (29 - 32)	**<0.001**
Hematocrit reduction (%)	2.70 ± 1.21 2.25 (1 - 6)	3.39 ± 1.76 3 (1 - 8)	1.09 ± 0.34 1 (0.5 - 2)	2.87 ± 0.92 2.8 (1.7 - 6)	**<0.001**
Need for blood transfusion	1 (3.33%)	3 (10.0%)	0 (0.0%)	2 (6.67%)	0.320
Postoperative hospital stays (days)	1.67 ± 0.55 2 (1 - 3)	2.20 ± 0.48 2 (1 - 3)	1.23 ± 0.43 1 (1 - 2)	1.97 ± 0.41 2 (1 - 3)	**<0.001**

Table 3: Second analysis of blood loss, operative time, and postoperative hospital stays

Dependent Variable			Mean Difference	P-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Intraoperative blood loss	Misoprostol Group	Oxytocin Group	-167.667	**<0.001**	-192.82	-142.52
		Carbetocin Group	153.833	**<0.001**	128.68	178.98
		Tourniquet Group	-58	**<0.001**	-83.15	-32.85
	Oxytocin Group	Misoprostol Group	167.667	**<0.001**	142.52	192.82
		Carbetocin Group	321.5	**<0.001**	296.35	346.65
		Tourniquet Group	109.667	**<0.001**	84.52	134.82
	Carbetocin Group	Misoprostol Group	-153.833	**<0.001**	-178.98	-128.68
		Oxytocin Group	-321.5	**<0.001**	-346.65	-296.35
		Tourniquet Group	-211.833	**<0.001**	-236.98	-186.68
	Tourniquet Group	Misoprostol Group	58	**<0.001**	32.85	83.15
		Oxytocin Group	-109.667	**<0.001**	-134.82	-84.52
		Carbetocin Group	211.833	**<0.001**	186.68	236.98
Total blood loss	Misoprostol Group	Oxytocin Group	-196	**<0.001**	-266.32	-125.68
		Carbetocin Group	172.167	**<0.001**	101.84	242.49
		Tourniquet Group	-66.333	0.072	-136.66	3.99
	Oxytocin Group	Misoprostol Group	196	**<0.001**	125.68	266.32
		Carbetocin Group	368.167	**<0.001**	297.84	438.49
		Tourniquet Group	129.667	**<0.001**	59.34	199.99
	Carbetocin Group	Misoprostol Group	-172.167	**<0.001**	-242.49	-101.84
		Oxytocin Group	-368.167	**<0.001**	-438.49	-297.84
		Tourniquet Group	-238.5	**<0.001**	-308.82	-168.18
	Tourniquet Group	Misoprostol Group	66.333	0.072	-3.99	136.66
		Oxytocin Group	-129.667	**<0.001**	-199.99	-59.34
		Carbetocin Group	238.5	**<0.001**	168.18	308.82
Operation time	Misoprostol Group	Oxytocin Group	-12.367	**<0.001**	-15.66	-9.07
		Carbetocin Group	17.733	**<0.001**	14.44	21.03
		Tourniquet Group	-5.133	**0.001**	-8.43	-1.84
	Oxytocin Group	Misoprostol Group	12.367	**<0.001**	9.07	15.66
		Carbetocin Group	30.1	**<0.001**	26.81	33.39
		Tourniquet Group	7.233	**<0.001**	3.94	10.53
	Carbetocin Group	Misoprostol Group	-17.733	**<0.001**	-21.03	-14.44
		Oxytocin Group	-30.1	**<0.001**	-33.39	-26.81
		Tourniquet Group	-22.867	**<0.001**	-26.16	-19.57

	Tourniquet Group	Misoprostol Group	5.133	**0.001**	1.84	8.43
		Oxytocin Group	-7.233	**<0.001**	-10.53	-3.94
		Carbetocin Group	22.867	**<0.001**	19.57	26.16
Postop. hospital stay	Misoprostol Group	Oxytocin Group	-0.533	**<0.001**	-0.85	-0.22
		Carbetocin Group	0.433	**0.003**	0.12	0.75
		Tourniquet Group	-0.300	0.071	-0.62	0.02
	Oxytocin Group	Misoprostol Group	0.533	**<0.001**	0.22	0.85
		Carbetocin Group	0.967	**<0.001**	0.65	1.28
		Tourniquet Group	0.233	0.227	-0.08	0.55
	Carbetocin Group	Misoprostol Group	-0.433	**0.003**	-0.75	-0.12
		Oxytocin Group	-0.967	**<0.001**	-1.28	-0.65
		Tourniquet Group	-0.733	**<0.001**	-1.05	-0.42
	Tourniquet Group	Misoprostol Group	0.300	0.071	-0.02	0.62
		Oxytocin Group	-0.233	0.227	-0.55	0.08
		Carbetocin Group	0.733	**<0.001**	0.42	1.05

Table 4: Second analysis of Hemoglobin (Hb) and Hematocrit (Hct) levels

Dependent Variable			Mean Difference	P-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Postoperative Hb	Misoprostol Group	Oxytocin Group	0.7633	**<0.001**	0.322	1.205
		Carbetocin Group	-0.5267	**0.013**	-0.968	-0.085
		Tourniquet Group	0.7567	**<0.001**	0.315	1.198
	Oxytocin Group	Misoprostol Group	-0.7633	**<0.001**	-1.205	-0.322
		Carbetocin Group	-1.29	**<0.001**	-1.732	-0.848
		Tourniquet Group	-0.0067	1.000	-0.448	0.435
	Carbetocin Group	Misoprostol Group	0.5267	**0.013**	0.085	0.968
		Oxytocin Group	1.29	**<0.001**	0.848	1.732
		Tourniquet Group	1.2833	**<0.001**	0.842	1.725
	Tourniquet Group	Misoprostol Group	-0.7567	**<0.001**	-1.198	-0.315
		Oxytocin Group	0.0067	1.000	-0.435	0.448
		Carbetocin Group	-1.2833	**<0.001**	-1.725	-0.842
Hb reduction	Misoprostol Group	Oxytocin Group	-0.7867	**<0.001**	-1.000	-0.574
		Carbetocin Group	0.4533	**<0.001**	0.240	0.666
		Tourniquet Group	-0.69	**<0.001**	-0.903	-0.477
	Oxytocin Group	Misoprostol Group	0.7867	**<0.001**	0.574	1.000
		Carbetocin Group	1.24	**<0.001**	1.027	1.453
		Tourniquet Group	0.0967	0.639	-0.116	0.310
	Carbetocin Group	Misoprostol Group	-0.4533	**<0.001**	-0.666	-0.240
		Oxytocin Group	-1.24	**<0.001**	-1.453	-1.027
		Tourniquet Group	-1.1433	**<0.001**	-1.356	-0.930
	Tourniquet Group	Misoprostol Group	0.69	**<0.001**	0.477	0.903
		Oxytocin Group	-0.0967	0.639	-0.310	0.116
		Carbetocin Group	1.1433	**<0.001**	0.930	1.356
Postoperative Hct	Misoprostol Group	Oxytocin Group	0.7867	0.093	-0.086	1.660
		Carbetocin Group	-1.4067	**<0.001**	-2.280	-0.534
		Tourniquet Group	0.7000	0.163	-0.173	1.573
	Oxytocin Group	Misoprostol Group	-0.7867	0.093	-1.660	0.086
		Carbetocin Group	-2.1933	**<0.001**	-3.066	-1.320
		Tourniquet Group	-0.0867	0.994	-0.960	0.786
	Carbetocin Group	Misoprostol Group	1.4067	**<0.001**	0.534	2.280
		Oxytocin Group	2.1933	**<0.001**	1.320	3.066
		Tourniquet Group	2.1067	**<0.001**	1.234	2.980

	Tourniquet Group	Misoprostol Group	-0.7000	0.163	-1.573	0.173
		Oxytocin Group	0.0867	0.994	-0.786	0.960
		Carbetocin Group	-2.1067	**<0.001**	-2.980	-1.234
Hct reduction	Misoprostol Group	Oxytocin Group	-0.6867	0.112	-1.477	0.103
		Carbetocin Group	1.6067	**<0.001**	0.817	2.397
		Tourniquet Group	-0.1667	0.946	-0.957	0.623
	Oxytocin Group	Misoprostol Group	0.6867	0.112	-0.103	1.477
		Carbetocin Group	2.2933	**<0.001**	1.503	3.083
		Tourniquet Group	0.5200	0.320	-0.270	1.310
	Carbetocin Group	Misoprostol Group	-1.6067	**<0.001**	-2.397	-0.817
		Oxytocin Group	-2.2933	**<0.001**	-3.083	-1.503
		Tourniquet Group	-1.7733	**<0.001**	-2.563	-0.983
	Tourniquet Group	Misoprostol Group	0.1667	0.946	-0.623	0.957
		Oxytocin Group	-0.5200	0.320	-1.310	0.270
		Carbetocin Group	1.7733	**<0.001**	0.983	2.563

Figure 1. Flowchart of the study.