

Intravenous carbetocin vs. uterine tourniquet to reduce blood loss in open myomectomy operation: A randomized clinical trial

Marwan Mohamed Gamal*, Sherif Fathy El-Mekawi, Ahmed Mohamed Bahaa El-Din, Rasha Mahmoud Medhat Abdul Hadi
Department of Obstetrics & Gynecology, Ain Shams University, Cairo, Egypt

SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · (B) Data Collection · (C) Statistical Analysis · (D) Data Interpretation · (E) Manuscript Preparation · (F) Literature Search · (G) No Fund Collection

Background: Carbetocin works as an oxytocic, antihemorrhagic and uterotonic drug in the peripheral nervous system. Carbetocin functions as an agonist at peripheral oxytocin receptors, particularly in the myometrium commonly known as a fibroid.

Aim of the Work: To compare the efficacy of intravenous 100 microgram carbetocin vs. uterine tourniquet to reduce intraoperative blood loss in open myomectomy.

Patients and Methods: This current study was a randomized controlled trial, carried out on 110 women who underwent myomectomy at Ain Shams University Maternity hospital. Group A included 55 of the patients who received 100 microgram of carbetocin IV intraoperative and Group B included 55 patients with uterine artery tourniquet was done.

Results: Reduction in Hemoglobin was significantly less in Group B than Group A ($p < 0.001$), with no significant difference between the two groups as regards Preoperative Hematocrit ($p = 0.50$). Postoperative Hematocrit, was significantly higher in Group B than Group A ($p < 0.001$). Reduction in Hematocrit was significantly less in Group B than in Group A ($p < 0.001$). The need for blood transfusion was not significantly different between the two groups ($p = 0.49$).

Conclusion: Despite proven by different studies that the use of carbetocin during open myomectomy whether intravenous or intramyometrial decreases the intraoperative blood loss, the use of uterine artery tourniquet in our study seems to be more effective method that significantly decrease bleeding and allows proper hemostasis during this operation.

Keywords: Intravenous carbetocin; Uterine tourniquet; Open myomectomy

Address for correspondence:

Marwan Mohamed Gamal,
Department of Obstetrics & Gynecology, Ain Shams University,
Cairo, Egypt
Tel: +201223936172, E-mail: marwan_15963@hotmail.com

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INTRODUCTION

Most fibroids are small and do not cause any problems. When they are detected it is usually by chance. Depending on where the fibroids are located they may cause period pain, heavy menstrual bleeding or other symptoms; Fibroids can be categorized depending on where they appear [1].

Myomectomy is the surgical removal of leiomyoma from the uterus, leaving the uterus in place [2].

There are three types of myomectomy: hysteroscopic myomectomy, laparoscopic myomectomy. Open myomectomy is the most invasive surgical procedure to remove fibroids [3].

Laparoscopic myomectomy has less pain and shorter time in hospital than open surgery. Small fibroids can be taken out using laparoscopy or hysteroscopy [4].

The ascending blood supply of the uterus is from the uterine arteries, which pass through the cardinal ligament. The descending blood supply is from the ovarian arteries, the uterine and ovarian vessels anastomose to perfuse the uterus [5,6].

Carbetocin (Pabal), or 1-butanoic acid-2-(O-methyltyrosine)-1-carboxyotocin, is an oxytocic and antihemorrhagic used to control hemorrhage particularly immediately following uterine incisions [7]. Carbetocin is an agonist at peripherally expressed oxytocin receptors [8].

Uterine tissues from non-pregnant women across all stages of the menstrual cycle had capacity to bind to oxytocin, Concentrations of binding sites for endometrium, myometrium and fibromyomas are different [6].

Nevertheless, oxytocin has a short half-life (4-10 minutes), necessitating continuous intravenous infusion. Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered as a single-dose injection, either intravenously or intramuscularly. Intravenously administered Carbetocin has a half-life of approximately 40 minutes, around 4-10 times longer than that reported for oxytocin [7].

Another study was Intravenous Carbetocin to decrease blood loss during open myomectomy, 86 women undergoing abdominal myomectomy for symptomatic uterine leiomyomas were randomly assigned to receive a single dose of pre-operative of IV 100 µg Carbetocin (n

= 43) or placebo (n = 43) just before the operation. The primary outcome was intra-operative blood loss. A single pre-operative dose of IV Carbetocin (100 µg) is a simple applicable method for reducing intra-operative blood loss and operative time in abdominal myomectomy [9,10].

Another Study carbetocin in the operation of myomectomy. A total of 54 patients under myomectomy were divided into 2 groups. The patients in test group were injected 100 µg carbetocin, and in control group were injected 20 U oxytocin into uterine after the myomectomy. Carbetocin may promote uterine contraction and reduce bleeding during the myomectomy [9].

Another study was on Carbetocin that was used before in gynecological purpose as injection during myomectomy to reduce blood loss and was published by; the aim of the pervious study was to observe the effect of intramyometrial carbetocin injection in reducing intraoperative blood loss during myomectomy and to study the possible postoperative benefits. The Study design was a randomized controlled trial [11].

Forty women with symptomatic uterine leiomyomata scheduled for myomectomy were recruited in the study. They were divided into two groups of 20 patients each. In the control group, hemostasis was performed with the uterine artery tourniquet technique. Meanwhile, in the study group, hemostasis was performed through an intramyometrial injection of carbetocin. Results were Injection of intramyometrial carbetocin was associated with less blood loss during myomectomy. Moreover, it may lower the need for blood transfusion. Patients in whom carbetocin was used showed lower drop in their hemoglobin and hematocrit levels when measured 48 h postoperatively. So Conclusion intramyometrial Carbetocin appears to be an effective drug in minimizing blood loss during myomectomy [11].

Ten to forty percent of patients will experience mild picture of some side effects like nausea (40%), vomiting (3%), abdominal pain (3%), itching skin (10%), increased body temperature (12%), trembling and weakness (2%) [12,13].

PATIENTS AND METHODS

Type of the Study: A randomized controlled clinical trial.

Study Setting: This clinical trial was conducted at Ain Shams University Maternity Hospital.

Study Time: Recruitment of data began from January 2018 to January 2020.

Study Population: All patients were recruited from those who attended the gynecology outpatient clinic at Ain Shams University Maternity Hospital.

Study Design:

Study Groups

Group A: Included 55 Patients who were admitted for an open myomectomy after obtaining informed consent.

Intervention: Those who received 100 microgram IV carbetocin intraoperative after entering abdominal cavity

Group B: Included 55 Patients who were admitted for an open myomectomy after obtaining informed consent.

Intervention: Application of uterine artery tourniquet after entering the abdominal cavity and before starting the myomectomy.

Randomization:

To insure that everyone had the chance of participation, randomization was performed using a computer generated randomization system.

Simple randomization: This technique maintains complete randomness of the assignment of a subject to a particular group using computer-generated random numbers.

Sample size justification: Using PASS program, setting α error 0.05 power of study 80%. Result from previous study, Sallam HF and Shady NW [10] showed that average carbetocin group the transfusion rate was 18.6% and is assumed that average tourniquet group to be 45% bas on this study in consideration 5% drop out rate, the needed sample 55 cases per group.

Inclusion Criteria:

1. Women undergo an open myomectomy due to heavy vaginal bleeding ± pressure related symptoms, infertility and recurrent pregnancy loss.
2. Age ranging from (20-40).
3. Women with BMI between 18.5-29.9 kg/m².
4. Single Intramural to sub mucous myoma ranging from 5 to 10 cm.

Exclusion Criteria:

1. Pregnancy
2. Previous laparotomy and previous caesarean section.
3. History of any side effects of carbetocin like nausea, vomiting, abdominal pain, itching, fever, chest pain, chills, sweating, metallic taste, allergy, tachycardia and respiratory distress [14].
4. Hemoglobin <10 g /dl, Platelets >150 cell/m³
5. Any associated medical comorbidity like known hypertension, Diabetes mellitus, and cardiovascular, renal or liver disease, bleeding tendencies.
6. Autoimmune Diseases, Sickle Cell Disease and bleeding tendency.

7. Rapidly growing fibroids or suspected leiomyosarcoma
8. Any patient needs other surgical procedure for any other associated condition e.g. adnexal pathology

All enrolled patients were subjected to the following:

History taking:

- Marital state, parity, menopause
- Past history bleeding
- Past history of menstrual irregularity
- Exclude some medical disorders like Hypertension, blood diseases, Cardiac disease, etc.)
- General examination: pulse, blood pressure, temperature and respiratory rate.
- Abdominal examination with particular emphasis on myoma contour and abdominal enlargement.
- Pelvic ultrasound, Trans vaginal ultrasound
- BHCG to document presence of pregnancy or not.
- Pre-operative Full lab investigations (CBC, liver function tests, kidney function tests, coagulation profile, Viral Markers: HBV – HCV- HIV).

Study interventions

All patients undergoing an open myomectomy were subjected to these steps:

1. Pre-operative anesthetic consultation.
2. Consent for myomectomy and its complications.
3. General anesthesia.
4. Senior Staff operated
5. IV Antibiotics before skin incision.
6. Sterilization, catheterization, TOWELING.
7. Pfannenstiel incision.

Group A received 100 microgram carbetocin intravenous after entry of the abdominal cavity, The anesthesiologist was notified before the injection of Carbetocin, Group B uterine tourniquet application was done.

The uterine vascular cutoff technique was done in steps, first, the bladder is dissected from the lower uterine segment; and then a perforation is made through the broad ligament at the level of the internal os. A tourniquet (Using 16-inch Foley catheter) is then passed through the perforation bilaterally, encircling the uterine arteries bilaterally and pulled up tight and grasped with an artery clamp, a tourniquet time was kept for 30 minutes, then released and reapplied after 5 minutes to re-establish blood flow and prevent irreversible damage to the uterine muscle cells.

For Both Groups after removal of uterine fibroid; the myoma bed was sutured by continuous locked suture *via* vicryl 0, then closure of myometrium baseball like suture

Then ensured hemostasis ± hemostatic sutures if needed for Group A. and for Group B after uterine tourniquet was released, intra peritoneal drain was left if needed.

Then closure of peritoneum *via* vicryl 2/0, Sheath *via* vicryl 1, ensured hemostasis then skin was closed by proline 2/0

Then each patient participated in the study was tested for the following end points:

1. Operative blood loss (measured by weighting towels starting after entered peritoneal cavity and started myomectomy operation)
2. Sucked blood measured.
3. Measuring the difference between preoperative and 24-hours-postoperative haematocrit.

Objectives:

Primary outcome:

Intraoperative blood loss; which was estimated by:

- Measuring amount of blood loss through suction machine.
- Measuring amount of blood loss through gauzes and suction machine.
- Large gauzes fully soaked 100 to 150 cc – moderate soaked 50 to 100 cc – minimal soaked 50 cc.
- Small gauzes fully soaked 25 cc – moderate soaked 15 cc – minimal soaked 5 cc.
- Sucked blood measured by excluding washing saline [13].

Measuring the difference between preoperative and 24-hours-postoperative haematocrit using the following formula:

$$\frac{EBV \times (Hi - Hf)}{Hi}$$

Where Hi is the preoperative blood hematocrit, Hf is the postoperative one and EBV is the estimated blood volume [14].

The estimated blood volume can be calculated by multiplying weight time's average blood volume which is around 65 mL/kg in females [13].

Secondary outcome:

1. Operative time.
2. Complications such as the need for blood transfusion.

Ethics: The study was approved from the Ethical Committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University.

Written Informed consent was taken from all participants before recruitment in the study after an explanation of the purpose and procedures of the study.

Statistical analysis: Descriptive statistics for measured variables were expressed as range, mean and standard deviation (for metric data); range, median and inter quartile range (for discrete data); and number and proportions (for categorical data). Demographic data, and primary and secondary outcomes of both groups were compared using t-test (for quantitative parametric measures), Mann-Whitney’s U-test (for quantitative non-parametric measures) and chi-squared and Fischer’s Exact tests (for categorical measures). Pearson’s correlation coefficient (for metric variables) and Spearman’s correlation coefficient (for rank variables) were used to estimate association between variables. Microsoft® Excel® (Version 2007) . Statistical analysis was performed using Statistical Package for Social Sciences (SPSS®) for Windows® version 16.0. (SPSS Inc., Chicago, IL, USA).

RESULTS

There is no significance between Mean between Carbetocin group and uterine tourniquet group as regard age and BMI

There is no significance between Number of patients between Carbetocin group and uterine tourniquet group as regard heavy vaginal bleeding, pressure related symptoms and recurrence pregnancy loss. But Patients suffer from infertility more in carbetocin group.

Tab. 1. shows no significance between Mean between Carbetocin group and uterine tourniquet group as hemoglobin and hematocrit but pulse was higher in uterine tourniquet group.

Tab. 2. shows significant decrease in mean hemoglobin in carbetocin group related to uterine tourniquet group post myomectomy, and no significance between Mean between Carbetocin group and uterine tourniquet group as pulse rate and towel weight post-operative.

There is no significance between Carbetocin group and uterine tourniquet group as Need for blood transfusion. Despite the study shows significant need to drain in carbetocin group in relation to uterine tourniquet group

Tab. 3. shows significant decrease of hemoglobin and hematocrit in carbetocin group post operatively in relation to preoperative hemoglobin and hematocrit, significant increase in pulse in the same group post operatively in relation to preoperative pulse, and also increase in towels weight post-operative in relation to pre-operative towels weight.

Tab. 4. shows significant decrease of hemoglobin and hematocrit in uterine tourniquet group post operatively in relation to preoperative hemoglobin and hematocrit, significant increase in pulse in the same group post operatively in relation to preoperative pulse, and also increase in towels weight post-operative in relation to pre-operative towels weight.

There is a statistically significant difference between two groups regarding amount of change in Hb level.

Tab. 1. Pre-operative data.	Carbetocin group (N=55)		Uterine Tourniquet group (N=55)		t*	P value
	Mean	SD	Mean	SD		
Hb PRE	10.74	0.76	10.83	0.76	0.58	0.57 NS
Ht PRE	32.18	2.22	32.47	2.29	0.69	0.50 NS
Pulse PRE	82.45	3.84	84.24	4.93	2.12	0.04 S
Towels Wt PRE	150.00	0.00	150.00	0.00	-	-
*Student t test						

Tab. 2. Post-operative data.	Carbetocin group (N=55)		Uterine Tourniquet group (N=55)		t*	P value
	Mean	SD	Mean	SD		
Hb POST	9.40	0.67	10.42	0.91	6.63	<0.001 HS
Ht POST	28.30	2.17	31.40	2.78	6.51	<0.001 HS
Pulse POST	90.36	8.82	89.53	7.78	0.53	0.60 NS
Towel Wt. POST	431.44	65.28	439.35	63.03	0.65	0.52 NS
*Student t test						

Tab. 3. Comparison between pre and post-operative data in Carbetocin group.	Mean	SD	t*	P value	
	Hb PRE	10.74			0.76
	Hb POST	9.40	0.67	15.08	<0.001 HS
	Ht PRE	32.18	2.22	13.17	<0.001 HS
	Ht POST	28.30	2.17		
	Pulse PRE	82.45	3.84	6.22	<0.001 HS
	Pulse POST	90.36	8.81		
	Towels Wt PRE	150.00	0.00	31.98	<0.001 HS
Towels Wt. POST	431.44	65.28			
*Paired samples t test					

Table 5 shows significant decrease of Mean hemoglobin in carbetocin group post operatively in relation to uterine tourniquet group post operatively (**Tab. 5**).

DISCUSSION

There are different ways to decrease blood loss during myomectomy may be surgical as uterine tourniquet involving utero-ovarian Vessels, or medical as vasopressin 20 U in 50-100 mL normal saline [15], Epinephrine also induces a vasoconstrictive effect on tissues, and used during gynecological operations [16]. The use of gonadotropin-releasing hormone (GnRH) agonists before myomectomy became popular [17]. Misoprostol, a prostaglandin E1 analogue, acts as a uterotonic and vasoconstrictor [18]. Carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus [19].

Thus the current study was held to assess the efficiency of use of Intravenous Carbetocin vs. Uterine Tourniquet to Reduce Blood Loss in Open Myomectomy Operation

In our study Group A included 55 women, while Group B included 55 women.

In our study there was no significant difference as regard patient characteristics (age, weight, BMI, Heavy Vaginal Bleeding, Pressure related symptoms, infertility and Recurrent pregnancy loss) between two groups.

Our results showed that Uterine Tourniquet significantly reduces bleeding during myomectomy than Intravenous Carbetocin. Group A hemoglobin: (9.8 ±.67 g/dl) was significantly less than Group B (10.42 ±.91g/dl) (p<0.001).

In our study there was significant statistical difference in the pulse before and after Myomectomy in the two groups.

In our study Postoperative Hemoglobin was significantly higher in Group B than Group A (p<0.001); Reduction in Hemoglobin was significantly less in Group B than Group A (p<0.001). Also postoperative hematocrit was significantly higher in Group B than Group A (p<0.001); reduction in hematocrit was significantly less in Group B than in group A (p<0.001).

These results in comparison with other studies, in the study of Sallam HF and Shady NW [10], who tested the use of 100 µg Carbetocin IV in open myomectomy on 43 women whereas the control group of 43 women who did not receive carbetocin, this study showed that 100 µg Carbetocin IV significantly reduced the quantity of blood loss (714.19 ± 186.27 ml) vs. (1033.49 ± 140.9 ml) in the control group (p <0.01).

Taher A, et al. [20] used the same method as Sallam HF and Shady NW [10] but worked on larger number of patients than Sallam and Shady, the result was supporting to Sallam and Shady.

Taher A, et al. [20], study showed that 100 µg Carbetocin IV significantly reduced the quantity of blood loss (436.9 ± 41.7 ml) in the carbetocin group vs. (621.5 ± 74.1 ml) in the placebo group (p <0.01), It also showed significantly drop of hemoglobin before and after myomectomy: (9.1 ± 0.8 g/dl) in the placebo group, (10.3 ± 0.6 g/dl) in the carbetocin group (p <0.01).

On the contrary of this study, Gad Allah SH, et al. [11] results showed that carbetocin is more efficient than tourniquet to control blood loss may be due to intramural use of carbetocin as Gad Allah studied usage of 200 µg carbetocin diluted in 50 ml of normal saline and injected intramyometrial on 20 women vs. the control group of 20 women in which hemostasis was performed with the uterine artery tourniquet technique, the study showed that 200 µg of diluted carbetocin in 50 ml of normal saline injected intramyometrial significantly reduce the quantity of blood loss (235 ± 128 ml) in comparison with (348 ± 279 ml) in the tourniquet group (p <0.04), It also showed significantly drop of hemoglobin before and after myomectomy (2.6 ± 0.2 mg/dl) in the tourniquet group, (1.1 ± 0.2 mg/dl) in the carbetocin group (p = 0.02).

Lotfy M, et al. [21] used a different approach to decrease the blood loss during open myomectomy through testing two groups, The first group was 66 women received 30 ml of sodium chloride with added to 50mg tranexamic acid IV intraoperative, whereas the second group was 66 women who received 30 ml of sodium chloride with added

Tab. 4. Comparison between pre and post-operative data in uterine tourniquet group.

	Mean	SD	t*	P value
Hb PRE	10.83	0.76	8.21	<0.001 HS
Hb POST	10.42	0.91		
Ht PRE	32.47	2.29	5.70	<0.001 HS
Ht POST	31.40	2.78		
Pulse PRE	84.24	4.93	4.72	<0.001 HS
Pulse POST	89.53	7.78		
Towels Wt PRE	150.00	0.00	34.04	<0.001 HS
Towel Wt. POST	439.35	63.03		

*Paired samples t test

Tab. 5. Comparison between two groups regarding change in Hb level.

Group		Hb PRE		Hb POST		Time		Group		Time*Group	
		Mean	SD	Mean	SD	F	P	F	P	F	P
Group	Carbetocin group	10.74	.76	9.40	.67	294.80	<0.001	15.33	<0.001	83.01	<0.001
	Uterine Tourniquet group	10.83	.76	10.42	.91						

Repeated measure ANOVA test

100 µg Carbetocin IV, this approach showed that 100 µg Carbetocin in 30ml sodium chloride IV significantly reduced the quantity of blood loss (399.27 ± 28.94 ml) rather than in the tranexamic acid group (535.15 ± 80.30 ml) ($p < 0.001$), It also showed significantly drop of hemoglobin before and after myomectomy: (9.95 ± 1.0 / dl) in the tranexamic acid group, (10.63 ± 1.01 g/dl) in the carbetocin group ($p < 0.001$).

Elhoussieny AS, et al. [22] tested 22 women by receiving 100 µg Carbetocin IV in the study group instead of 22 women in the control group who received 400 µg misoprostol vaginally, one hour preoperative.

However all the previous mentioned studies support usage of carbetocin to decrease blood loss in myomectomy, Elhoussieny AS, et al. [22] study showed no significant differences between women of both groups regarding estimated blood loss, postoperative Hb, postoperative HCT, calculated estimated blood loss, need for blood transfusion and hospital stay ($P > 0.05$) as follow post-operative hemoglobin (10.74 ± 1.29 g/dl) in the misoprostol group *vs.* (10.62 ± 1.35 g/dl) in the carbetocin group ($p = 0.769$), It may be due to different technique.

On the other hand Shen Y, et al. [23] used 100 µg Carbetocin IV on the study group of 30 women and used IV oxytocin on 28 women. The 100 µg Carbetocin IV significantly reduced the quantity of blood loss (111 ± 35 ml) in the carbetocin group *vs.* (160 ± 49 ml) in the oxytocin group ($p < 0.01$).

So Sallam HF and Shady NW [10]; Gad Allah SH, et al. [11]; Taher A, et al. [20]; Lotfy M, et al. [21] and Shen Y, et al. [23] Studies' results came in favor of the usage of carbetocin to decrease blood loss during myomectomy.

However Elhoussieny AS, et al. [22] study showed that there was no difference between carbetocin and misoprostol in decreasing blood loss.

CONCLUSION

Despite proven by different studies that the use of carbetocin during open myomectomy whether intravenous or intramyometrial decreases the intraoperative blood loss, the use of uterine artery tourniquet in our study seems to be more effective method that significantly decrease bleeding and allows proper hemostasis during this operation.

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