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ORIGINAL ARTICLE

Intraoperative carbetocin to decrease blood loss during hysteroscopic myomectomy: a randomized controlled pilot trial.

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ABSTRACT

Background and Aim: Uterine fibroids are common benign female neoplasms which are frequently managed by myomectomy to preserve fertility. It is a bloody procedure due its rich blood supply. The application of uterotonics, like oxytocin, has been recommended to decrease blood loss. Carbetocin is a synthetic analogue of oxytocin, that has a more rapid onset and prolonged action. This study was conducted to evaluate the effect of carbetocin as an utero-tonic agent on reducing blood loss during hysteroscopic myomectomy.

Patients and Methods: We included 40 women with submucous myomas and scheduled for hysteroscopic myomectomy in this prospective randomized trial. They were randomly assigned into two groups; Group A received IV carbetocin (1 ml), and Group B (placebo). Intraoperative bleeding was classified as mild, moderate, and severe, whereas the quality of operative field was classified as good, fair, or poor.

Results: Both patient and disease criteria were statistically comparable between the two study groups. However, operative time was significantly prolonged in Group B (33.2 vs. 30.35 minutes in the other group – p = 0.044). The amount of intraoperative bleeding was significantly increased in the same group (p = 0.038). Although preoperative hemoglobin and hematocrit values were comparable between the two groups, both parameters showed a significant decline in the placebo group. Both the quality of operative field and surgeon satisfaction were significantly improved with carbetocin administration.

Conclusion: Carbetocin administration is recommended during hysteroscopic myomectomy to decrease blood loss and improve surgeon satisfaction.

Keywords: Carbetocin; Bleeding; Hysteroscopic myomectomy.

INTRODUCTION:

Uterine fibroids (myoma) are commonly encountered in daily gynecological practice. It is the most common benign female neoplasm during the reproductive period [1]. It arises from the uterine smooth muscle cells [2]. Although it is benign in nature, it could cause serious manifestations (bleeding and infertility) along with an impaired quality of life [3].

Uterine fibroids are best managed by myomectomy in ladies presenting with symptomatic lesions and needing fertility preservation [4]. These procedures could be performed via the open approach [5], laparoscopy [6], hysteroscopy [7], and robotic interventions [8] based on patient selection and disease criteria [9].

Currently, the hysteroscopic approach has proved its efficacy in managing small submucous lesions (below 4 or 5 cm in diameter) with low morbidity, shorter hospital stays, and better patient satisfaction [10]. The procedure could be also done in an outpatient setting in selected patients [11]. Moreover, it is safe for future pregnancy, with nearly 0% uterine perforation risk

[12]. However, the myomectomy procedure is a bloody procedure, as the fibroid receives its blood supply from the surrounding numerous arterioles and venules [13]. This could lead to hypovolemia, exaggeration of the preexisting anemia, need for blood transfusion, coagulation abnormalities, prolonged hospitalization periods, and increased healthcare costs [14, 15].

Multiple methods have been recommended to decrease bleeding during myomectomy procedures, including pharmacological (uterotonics) and non-pharmacological ones (uterine artery clipping) [16]. Nonetheless, no certain method has been specified to be the standard one. This could be explained by different approaches and lesion characteristics. The ideal method should be safe, effective, available, tolerable, and cost-effective [17].

Among the most popular methods, oxytocin administration is recommended by many gynecological surgeons as it is a uterotonic agent that decreases blood loss during hysterectomy, myomectomy, and endometrial resection procedures [18]. It could perform its action via stimulating oxytocin receptors which is present in both gravid and non-gravid uterus [19]. Despite the previous facts, some researchers found that oxytocin was ineffective in reducing blood loss during myomectomy procedures [20, 21]. This could be due to its short half-life, receptor saturation, or the incidence of side effects (hypotension or coronary spasm) [22].

Carbetocin is a synthetic analogue of oxytocin, which has a rapid onset and more prolonged action compared to the traditional pharmaceutical. Its half-life is ten times compared to oxytocin [23]. It could be administered through the intravenous of intramyometrial routes [15]. Few studies have evaluated the role of carbetocin on the perioperative outcomes in patients undergoing hysteroscopic myomectomy [24, 25], and these authors handled other approaches rather than the hysteroscopic one. Therefore, the current investigation was performed to evaluate the effect of carbetocin on reducing blood loss during hysteroscopic myomectomy.

METHODS:

The current randomized controlled pilot study was conducted at Mansoura University Obstetrics and Gynecology Department, after approval from the Institutional Review Board (IRB) of our medical school (IRB code: MS. 20.07.1178).

We included 40 women aged between 18 and 45 years, and diagnosed with a single submucous myoma of 4 cm or less, and a myometrial free margin of one cm at least. We included only type 0 or I lesions according to the FIGO classification [26]. These cases were collected and performed over the period of one year, from January to December 2021. We excluded women with other structural uterine anomalies (septum), myoma not meeting the previous criteria, uncontrolled systemic comorbidities, bleeding diathesis, previous gonadotropin-releasing hormone therapy, or known allergy to carbetocin.

The included ladies were randomly assigned to two groups; Group A included 20 patients who received intramyometrial carbetocin, and Group B included the remaining 20 patients who received placebo. All patients received the standard preoperative assessment including proper history taking, gynecological examination, and routine preoperative laboratory investigations (especially hemoglobin level and hematocrit value). In addition, all patients were assessed by transvaginal ultrasound (TVUS) to assess the number and size of myoma, as well as the myometrial free margin, defined as the distance between the outer border of myoma, and the inner aspect of uterine serosal layer. Both groups had signed informed written consent before the procedure after explaining the pros and cons of each intervention. Also, the study was done according to the Code of Ethics of World Medical Association (Declaration of Helsinki).

The hysteroscopic myomectomy procedure was performed when the patient was in the proliferative phase. General anestehsia was applied in all patients. After induction, patients in Group A received carbetocin 1 ml (100 mcg/ml which is the optimal carbetocin dose [27] over one minute whereas Group B received normal saline (1 ml over one minute). The procedure was done via the standard hysteroscopic setup. Initially, the uterine cavity was instilled with glycine 1.5% solution for proper visualization. A drape was inserted beneath the patient during the operation to collect the fluid escaping between the hysteroscopic sheath and the surrounding cervix, and to prevent its spillage. Fluid inflow an outflow was regularly checked every five minutes, and the procedure was terminated if the fluid imbalance reached 1 L.

The myomectomy was done via a monopolar resectoscope. The wire loop was used to remove the excised tissue fragments under vision; it was removed chip by chip till complete tissue extraction. At the end of the procedure, the surgeon was asked to rate the amount of intraoperative bleeding into mild, moderate or severe, and to report his opinion regarding the

quality of operative field view as good, fair, or poor. The previous two parameters were subjectively assessed as recommended by the study conducted by Mohamed et al. [28]. In addition, time needed for the procedure was estimated and recorded. The satisfaction of the surgeon was classified on a four-grade Likert scale; excellent, good, fair, and poor [29].

The patients were transferred to the recovery room then to the internal ward, where frequent monitoring was done. Another complete blood count test (CBC) was ordered for all patients before discharge. Their hemoglobin and hematocrit values were recorded to be compared with their baseline values. All patients were discharged on the first post-procedural day.

Our primary outcome was the surgeon rating of intraoperative bleeding, while secondary outcomes included operative time, hemoglobin and hematocrit changes, fluid deficit, surgeon rating of operative field quality, and occurrence of complications.

STATISTICAL ANALYSIS:

Our data was collected and tabulated using the Excel software, while it was analyzed via the SPSS software (version 26 for Windows, 2018). Categorical data were expressed as numbers and percentages and compared via the Chi-square test (or Fisher Exact test). Numerical data were presented as mean and standard deviation if they were normally distributed, while presented as median and range if abnormally distributed. These two data types were compared by the student-t and Mann-Whitney tests respectively. For all the previously mentioned tests, a p-value less than 0.05 was considered significant.

RESULTS:

Starting with patient demographics, in Groups A and B, the average age of the participants was 36.75 and 38 years, respectively. In the same two groups, their BMI had mean values of 29.6 and 29.4 kg/m2. Regarding the previous obstetric history, nulliparas represented 20% and 25% of patients in the same study groups, while the remaining women ha at least one parity. In terms of the preceding parameters, there was no significant difference between the two groups ($p > 0.05$). Table 1 shows the previous data.

Table (1): Sociodemographic data in the two study groups.

Items	Group A [Carbetocin group] (n= 20)	Group B [Placebo group] (n= 20)	Test of significance
Age (Years)	36.75 ± 5.05	38 ± 4.86	t = - 0.798 P= 0.430
BMI (Kg/m^2)	29.60 ± 1.97	29.40 ± 1.64	t = 0.350 P= 0.728
Parity			
Nullipara	4 (20%)	5 (25%)	MC= 1.606 P= 0.234
P1	1 (5%)	3 (15%)	
P2	6 (30%)	6 (30%)	
P3	8 (40%)	3 (15%)	
P4	1 (5%)	2 (10%)	
P5	0 (0%)	1 (5%)	

Abnormal uterine bleeding was reported by 75% and 65% of patients in Groups A and B respectively, whereas the remaining cases were complaining of infertility. All cases had single myoma. Most of the included myoma was type I (70% in both groups), while the remaining cases had type 0 lesions. The included myomas had mean values of 2.77 and 2.6 cm in the same study groups respectively. The uterine fundus was the most common site affected with fibroids (50% and 35% in the same groups). In addition, anterior wall lesions represented 20% and 25% of cases, while posterior wall lesions were present in 15% and 30% of cases respectively. Furthermore, fund anterior fibroids were present in 10% of cases in both study groups while ventroposterior lesion was present I only one case in Group A (5%). As shown in table 2,

Table (2): Clinical data in the two study groups.

Items	Group A [Carbetocin group] (n= 20)	Group B [Placebo group] (n= 20)	Test of significance
Presentation			
AUB	15 (75%)	13 (65%)	$\chi 2$= 0.473 P= 0.490
Infertility	5 (25%)	7 (35%)	
FIGO classification			
Type zero	6 (30%)	6 (30%)	$\chi 2$= 0 P= 1
Type one	14 (70%)	14 (70%)	
Size of myoma (cm)	2.77 ± 0.40	2.60 ± 0.32	t = 1.526 P= 0.135
Number of myoma			
Single	20 (100%)	20 (100%)	$\chi 2$= 0 P= 1
Site of myoma (ultrasound)			
Anterior wall	4 (20%)	5 (25%)	MC= 2.641 P= 0.620
Fundal	10 (50%)	7 (35%)	
Fundo-anterior	2 (10%)	2 (10%)	
Fundo-posterior	1 (5%)	0 (0%)	
Posterior wall	3 (15%)	6 (30%)	

The two groups expressed no significant difference regarding all the previous parameters (p > 0.05).

In Groups A and B, the mean procedure time was 30.35 minutes and 33.2 minutes, respectively, with the former showing a considerable decrease. Cervical dilation occurred in 3.65 and 3.7 minutes in the same two groups respectively. Regarding intraoperative bleeding, mild bleeding was more encountered with carbetocin administration (p = 0.038). Fluid deficit had mean values of 2.1 and 219.5 ml in the same two groups, respectively, which was comparable between the two groups (p > 0.05) (Table 3).

Table (3): Analysis of operative data in the two study groups.

Items	Group A [Carbetocin group] (n= 20)	Group B [Placebo group] (n= 20)	Test of significance
Operative time (min)	30.35 ± 4.63	33.2 ± 3.99	t = - 2.085 P= 0.044*
Cervical dilation time (min)	3.65 ± 1.15	3.70 ± 0.73	t = - 0.146 P= 0.885
Infusion volume (ml)	1642.50 ± 521.96	1850 ± 225.95	t = -1.632 P= 0.111
Intraoperative bleeding			
Mild	17 (85%)	11 (55%)	FET = 4.286 P = 0.038*
Moderate	3 (15%)	9 (45%)	
Fluid deficit (ml)	201 ± 54.18	219.50 ± 22.12	t = -1.414 P= 0.166

The two groups' preoperative hemoglobin levels were statistically comparable (p = 0.456). Nonetheless, the placebo group expressed significantly lower values compared to intervention one after the procedure (p = 0.019). On intragroup comparison, hemoglobin levels showed a significant drop in the placebo group compared to its baseline value (p = 0.005) (Table 4).

Table (4): Analysis of preoperative and postoperative hemoglobin level in the two study groups

Items	Group A [Carbetocin group] (n= 20)	Group B [Placebo group] (n= 20)	Test of significance
Preoperative hemoglobin (gm/dl)	11.53 ± 1.50	11.25 ± 0.72	t = 0.754 P= 0.456
Postoperative hemoglobin (gm/dl)	11.39 ± 1.46	10.53 ± 0.57	t = 2.444 P= 0.019*
P value	0.648	0.005*	

Although preoperative hematocrit values showed no significant difference between the study groups (36.46 and 34.13% in groups A and B respectively – p = 0.099), post-operative levels showed a significant increase in association with carbetocin administration (35.86 and 32.5% in groups A and B respectively – p = 0.024). On intragroup comparison, hematocrit values showed no changes when comparing pre, to post-operative levels (p = 0.240 and 0.122 in the same two groups respectively) (Table 5).

Table (5): Analysis of preoperative and postoperative hematocrit in the two study groups

Items	Group A [Carbetocin group] (n= 20)	Group B [Placebo group] (n= 20)	Test of significance
Preoperative hematocrit (%)	36.46 ± 5.76	34.13 ± 2.21	t = 1.690 P= 0.099
Postoperative hematocrit (%)	35.86 ± 5.97	32.50 ± 2.29	t = 2.356 P= 0.024*
P value	0.240	0.122	

Visual field showed a significant improvement in Group A (p = 0.039). It was good in 80% and 50% of cases, while it was fair in 20% and 25% of cases in Groups A and B respectively. Visual field was classified as "poor" in five patients in Group B (25%), compared to no cases in the other group. Additionally, surgeon satisfaction showed a significant improvement in the carbetocin group (Table 6).

Table (6): Visual field and surgeon satisfaction in the two study groups.

Items	Group A [Carbetocin group] (n= 20)	Group B [Placebo group] (n= 20)	Test of significance
Visual field			
Good	16 (80%)	10 (50%)	MC= 6.496 P= 0.039*
Fair	4 (20%)	5 (25%)	
Poor	0 (0%)	5 (25%)	
Surgeon satisfaction			
Excellent	7 (35%)	2 (10%)	MC= 4.863 P= 0.182
Good	6 (30%)	8 (40%)	
Fair	6 (30%)	6 (30%)	
Poor	1 (5%)	4 (20%)	

DISCUSSION:

The current study was conducted at Mansoura University Hospitals aiming to evaluate if carbetocin administration would have a beneficial impact on the perioperative outcomes of hysteroscopic myomectomy. To the best of our knowledge, there are few research that deal with the prior viewpoint. That poses an advantageous point in favor of our research. Nonetheless, its efficacy in the prevention of postpartum hemorrhage have been elucidated in multiple previous studies [30, 31].

On looking at our preprocedural data, one could notice no significant difference between the two groups regarding all of these data. This indicates the proper randomization technique, and that should also nullify any bias that might have skewed the results in favor of one group rather than the other one.

Our findings showed that carbetocin administration was associated with a significant decrease in the degree of intraoperative bleeding. Moreover, patients in the carbetocin group maintained their hemoglobin and hematocrit levels compared to the placebo group.

The beneficial effects of oxytocin and its analogues in myomectomy procedures are contradictory [32]. Carbetocin, the newer synthetic oxytocin analogue, could provide a more prolonged oxytocic action, with no need for prolonged or repeated infusions. Its structural properties prevent its early decomposition by aminopeptidase, oxidoreductase, and disulfidase [33].

It induces stimulation of oxytocin receptors leading to uterine contraction and subsequent vascular compression and decreased tissue perfusion. Moreover, these receptors are also present in the myometrial blood vessels. Its stimulation induces an increased vascular tone and decreased blood loss. These actions will eventually lead to decreased intraoperative blood loss and blood transfusion requirements [25].

In a previous study evaluating the effect of IV cerbetocin (100 mg) on perioperative outcomes of abdominal myomectomy operations, the authors included 69 patients in each of the intervention and placebo groups. Although most preoperative outcomes showed no significant difference between the two groups ($p > 0.05$), the carbetocin group showed a marked decline in blood loss and the need for blood transfusion. The former had mean values of 436.9 and 621.5 ml, while the latter was needed in 11.6% and 24.6% of cases in the intervention and placebo groups respectively. Additionally, carbetocin administration was associated with higher post-operative hemoglobin levels [15]. The authors concluded that IV carbetocin was an effective method in decreasing blood loss during abdominal myomectomy procedures.

Sallam and Shady reported that IV administration of the same previous dose of carbetocin led to as significant decrease in blood loss during open myomectomy (414.19 vs. 1033 ml in controls – $p < 0.001$). Nonetheless, the two study groups did not express significant differences between them regarding post-operative hemoglobin levels ($p = 0.069$) [34].

Moreover, Yang et al. and Wang et al. agreed with our findings as regards minimizing intraoperative bleeding, and lower drops in postoperative hemoglobin levels [23, 35].

Figure (23): Intraoperative views of submucous myomas using diagnostic hysteroscopy.

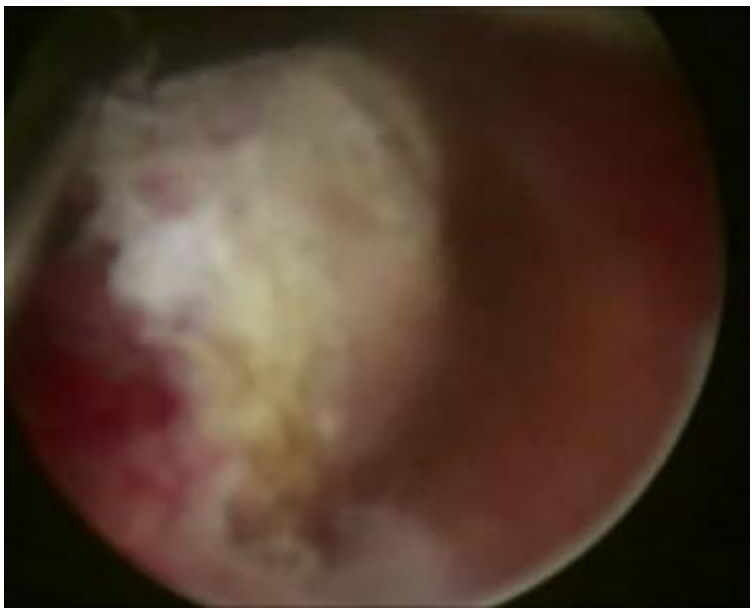

Figure (24): Intraoperative view of a control case (using saline) with moderate bleeding and unsatisfying surgical field.

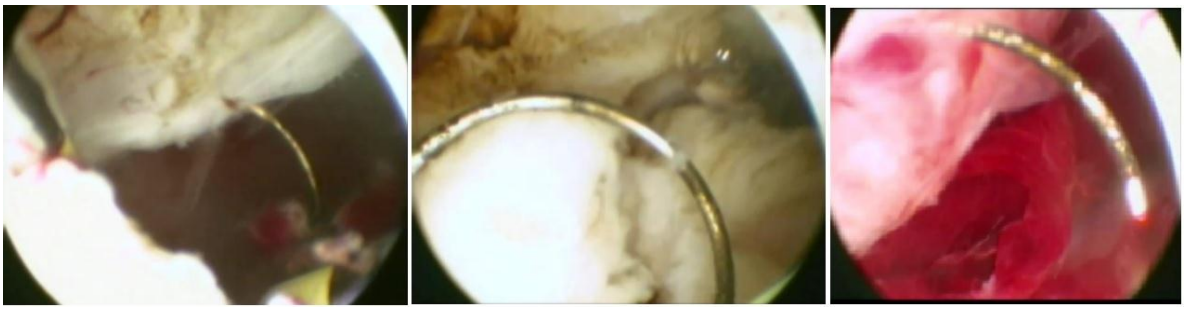

Figure (25): Good visual field with minimal bleeding during hysteroscopic myomectomy while using carbetocin.

A previous Egyptian study conducted at Cairo University agreed with our findings as intramyometrial carbetocin administration led to a significant decrease in intraoperative blood loss ($p = 0.04$). It had mean values of 235 ± 128 and 348 ± 279 ml in the carbetocin and placebo groups respectively. Besides, both hemoglobin and hematocrit values showed more drop in the placebo group compared to the intervention one. Hemoglobin drop had mean values of 1.1 and 2.6 gm/dl, while hematocrit drop had mean values of 3.25% and 7.89% in the same two groups respectively, with a significant difference between the two groups on statistical analysis ($p < 0.05$) [25].

Additionally, Mohamed et al. reported that intramyometrial injection of carbetocin led to a significant decline in blood loss during myomectomy procedures (177.43 vs. 288 ml in controls). The same group showed better stabilization of its hemoglobin and hematocrit parameters compared to their baseline values before the operation [36]

All of the previous studies confirm the positive role played by carbetocin administration in the reduction of intraoperative blood loss and stabilization of patient hematological parameters.

In the current study, the time of the hysteroscopic procedure showed a significant decline with carbetocin administration. Honestly, during the hysteroscopic procedure, the uterine contractions induced by carbetocin made the myoma lesion more prominent, which made the procedure technically easier.

Likewise, Yang et al. agreed with our findings regarding the decreased operative time with carbetocin administration. The authors reported that decreased intraoperative blood loss made the procedure easier, and thus, consuming less time [23].

Contrarily, Gad Allah et al. reported no significant difference between the carbetocin and control groups regarding the duration of the hysteroscopic myomectomy procedure ($p = 0.173$), which had mean values of 65 and 60 minutes in the intervention and control group respectively [25].

Heterogenicities between studies could be attributed to different surgical expertise, surgical approach, and operative ergonomics.

In the current study, we noted a significant improvement of the visual field in the carbetocin group. This was secondary to the decreased blood loss in the same group. Of course, improved surgeon satisfaction would be a natural consequence of the previous two findings.

Despite the unique perspective handled in the current investigation, it has some limitations. It was conducted in a single gynecological center, and the included sample size was relatively small. We only included patients who underwent hysteroscopic myomectomy rather than other approaches, which could weaken the generalizability of our findings. Therefore, more studies including more cases from different gynecological centers should be conducted soon.

Conclusion:

Based on the previous findings, the intravenous administration of carbetocin has a significant positive impact on the perioperative outcomes of hysteroscopic myomectomy procedure. It is associated with shorter operative time, better operative field quality, less blood loss, minor hemoglobin changes, and better surgeon satisfaction. Its application is strongly recommended in such a setting.

Conflict of interest:

None.

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