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Intravenous versus intramyometrial injection of carbetocin for reduction of blood loss during myomectomy operation

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Abstract---Background: Leiomyomas cause significant morbidity due to abnormal uterine bleeding and pelvic pressure symptoms. Carbetocin is a long-acting synthetic agonist analogue of the human oxytocin which induces uterine contractions. The study aims to compare intravenous carbetocin clinical effect and its myometrial injection to decrease blood loss in myomectomy operation. Methods: This randomized controlled study involved 60 patients who clinically and sonographically diagnosed with single intramural fibroids. Patients were allocated into three equal groups: Group A (Intravenous cabetocin group), group B (Myometrial carbetocin group) and group C (Control group). All patients underwent abdominal ultra-sonography, routine laboratory investigation. Results: The blood loss was more in-group B than the group A with high significant difference between the three groups ($P < 0.001$). Preoperatively there was significant difference in Hb between the three groups (0.002), but postoperatively there was insignificant difference in Hb between the three groups both groups. Conclusions: The use of intravenous carbetocin injection during preoperative abdominal myomectomy operation is more effective in decreasing the blood loss, shorter operative time, decreasing blood

transfusion and rapid postoperative recovery than the use intramyometrial Carbetocin injection.

Keywords--intravenous injection, intramyometrial injection, carbetocin, blood loss, myomectomy operation.

Introduction

Uterine fibroids (also known as leiomyomas or myomas) are the commonest benign uterine tumors, with an estimated incidence of 20%–40% in women during their reproductive years [1, 2]. They are monoclonal tumors of the uterine smooth muscle cells and consist of large amounts of extracellular matrix that contain collagen, fibronectin, and proteoglycan [3, 4]. Uterine fibroids may also cause menometrorrhagia, anemia, dysmenorrhea, dyspareunia, chronic (pelvic and back) pain, bloating, pelvic fullness, constipation, tenesmus, infertility, hydronephrosis, and urinary frequency [5]. Most women with uterine fibroids either remains asymptomatic or develops symptoms gradually over time. When patients are symptomatic, the number, size, and/or location of fibroids are critical determinants of its clinical manifestations. Commonly reported symptoms include heavy menstrual bleeding, dysmenorrhea, noncyclic pain, urinary symptoms, fatigue, and constipation [6, 7].

Leiomyomas cause significant morbidity due to abnormal uterine bleeding and pelvic pressure symptoms. Hence, they have great impact on the quality of life of many women and the healthcare system in general [8]. The incidence of leiomyoma's is up to three-fold greater in black women, who develop these tumors at earlier ages than white females. Uterine fibroids become clinically apparent in only up to 40% of women aged 40 years and over. Also, their incidence based on histology is more than twice the clinical incidence [8, 9]. Radiologically guided arterial myoma embolization was the first nonsurgical, nonmedical treatment approach to fibroid treatment, while oral contraceptive pills have been used to treat myoma-related symptoms such as bleeding and dysmenorrhoea, their effect is usually based on their suppression/regulation of the menstrual cycle. Medications include Gonadotropin-releasing hormone (GnRH) agonists, Progestin-releasing intrauterine device (IUD), and Tranexamic acid (Lysteda, Cyklokapron) [10, 11], the standard treatment for symptomatic uterine fibroids has always been surgical, either hysterectomy or, in women who wish to preserve their fertility, the more conservative procedure of myomectomy [12].

Fibroids represent one of the most frequent indications for major surgery in premenopausal women and as such, they constitute a major public health cost [13]. Myomectomy can be carried out via hysteroscopy, laparoscopy, or classically as an abdominal procedure. Bleeding during myomectomy is one of the major complications which can result in significant morbidity and mortality [14, 15]. Carbetocin is a long-acting synthetic agonist analogue of the human oxytocin. When injected to a woman, it induces uterine contractions. This medicine is stable at 30°C for 3 years, at 40°C for 6 months, at 50°C for 3 months and at 60°C for 1 month [16]. Carbetocin is a significant contributor to severe maternal morbidity and long-term disability, as well as to a number of other severe

maternal conditions, associated with more substantial blood loss, including severe anemia. The aim of the study is to compare the clinical effect of the intravenous carbetocin and its myometrial injection to decrease blood loss in myomectomy operation.

Patients and Methods

This randomized controlled study was carried out on 60 patients were clinically and sonographically diagnosed with single intramural fibroids. 4cm or more in diameter, and had symptoms like heavy menstrual flow, irregular bleeding, or infertility. The study was done at Obstetrics and Gynecology Department of Tanta University Hospital in the period from October 2019 to February 2021. Written consent from all patients was taken. The study was done after approval from the Ethical Committee Tanta University Hospitals, Tanta, Egypt. Exclusion criteria were patients received any hormonal treatment before the study, with bleeding disorders, with previous uterine surgery, cervical and broad ligament myoma, hypersensitivity to Oxytocin or Carbetocin,, anticoagulants treatment and pre-existing chronic diseases. Patients were allocated into three equal groups: Group A (Intravenous cabetocin group), group B (Myometrial carbetocin group) and group C (Control group). All patients were subjected to per-operative assessments [history taking, general and vitals examination, abdominal examination, abdominal ultra-sonography, routine Laboratory investigation (fasting blood sugar, ABO typing, hepatitis B virus marker and hepatitis C virus marker, complete urine analysis, SGOT, SGPT, serum urea, serum creatinine and coagulation profile)].

Interventions

Anaesthesia

The anaesthesia in all operations is general anaesthesia with Atracurium Besylate, Fentanyl and propofol (Diprivan).

Procedure

All myomas were removed by the same procedure using a pfannenstiel skin incision. Anterior abdominal wall incision in layers superficial fascia (fatty and membranous). Deep fascia, anterior rectus sheath rectus abdominis muscle, transversalis fascia, extra peritoneal connective tissue, and peritoneum. With catherizations hemostasis. Delivery and palpate the uterus then uterus to locate the leiomyoma.

Group A (Intravenous carbetocin): Carbetocin 100 µg (Papal: ferring Pharmaceutical, Copenhagen, Denmark) + Ringer's lactate solution 10 mL was injected directly and slowly into the vein over two minutes before uterine incision for myoma extraction. Careful planning and placement of midline uterine incision then removal of myoma by extending down. The uterine incision was done through the myometrium and entire fibroid pseudo capsule. The least vascular plane can be reached by extending this incision just deep to the capsule after the myoma is initially visualized. The myoma will then clearly be visible and may bulge slightly. Then surgeons put traction on the myometrial edges with Allis

clamps to expose the myoma. The myomas are then unchelated by grasping them with a single tooth tenaculum or towel clamp. The plane between the myometrium and myoma is typically dissected bluntly by using a sponge or the back end of an empty knife handle. The uterine defects are closed with sutures in layers, if the myometrial defect is deep (> 2 cm), two layers may be needed to approximate the tissue and achieve hemostasis. In our study, we used a size 0 polyglactin 910 (Vicryl TM) suture for the myometrium. The serosa was closed with a running suture; we used size 2 – 0 polydioxanone (PDSTM).

Group B (Myometrial carbetocin): Carbetocin 100 µg will be injected directly into the myometrium around the myoma before uterine incision for myoma extraction. Anterior abdominal wall incision in layers superficial fascia (fatty and membranous). Deep fascia, anterior rectus sheath rectus abdominis muscle, transversalis fascia, extra peritoneal connective tissue, and peritoneum. With catheterization hemostasis. Delivery and palpate the uterus then uterus to locate the leiomyoma. Carbetocin 100 µg will be injected directly into the myometrium around the myoma before uterine incision for myoma extraction. this step done by scrub nurse while preparing for operative instruments and placed on the surgical instrument table, when exploration of the uterus and the myoma required to be removed is done, the scrub nurse handles the syringe to the operating doctor who then inject the substance into the multiple sites intramyometrial in circumferential manner 1- 2 cm away from the margins of the myoma in the planned uterine incision site just before uterine incision for myoma extraction. Care was taken to avoid intravascular injection; the surgeon would withdraw the plunger of the syringe to check for blood. The anesthesiologist was always notified before the injection. Careful planning and placement of midline uterine incision then Removal of myoma by extending down. The myoma were removed as mentioned before in the group A and also, the closure of the uterine incision.

Group C (Control group): Myomectomy will be done without use of medications. Anterior abdominal wall incision was done in layers the same as mentioned before. Delivery and palpate the uterus then uterus to locate the leiomyoma. Myomectomy was done without use of medications. Careful planning and placement of midline uterine incision then Removal of myoma by extending down. The myoma were removed as mentioned before in the previous two groups and also, the closure of the uterine incision. Primary outcomes were intra-operative blood loss – estimated by measuring the amount of blood in the suction machine, in addition to the difference in the weight of surgical towels before and after surgery, the need for blood transfusion and change in hemoglobin and hematocrit levels before and 24 h after operation. Secondary outcomes were operative time, postoperative hospital stay and needing for ICU admission.

Statistical analysis

Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and were compared by paired Student's t- test for the same group. Qualitative variables were presented as frequency and percentage (%). Evaluation of diagnostic performance sensitivity, specificity, positive predictive value (PPV) and

negative predictive value (NPV). Agreement: Measurements of TTE and EC were compared by paired Student's T test. Calculation of Bias and its SD between TTE and EC were calculated. Modified Bland Altman plots of TTE and EC measurements were done A two tailed P value < 0.05 was considered significant.

Results

There was no significant difference in age between the three groups. There was significant difference in the body weight and myoma size between the three groups ($p=0.002$ and 0.005 respectively). Table 1

Table 1
Demographic data of the studied cases

	Group A (n=20)	Group B (n=20)	Group C (n=20)	p
Age (years)	34.70 $\pm$ 4.28	34.05 $\pm$ 3.72	33.2 $\pm$ 4.69	0.538
Weight	74.20 $\pm$ 5.71	68.35 $\pm$ 5.18	69.30 $\pm$ 5.25	0.002*
Sig. bet. grps	$p_1=0.003^*$, $p_2=0.015^*$, $p_3=0.843$			
Myoma size (cm)	7.20 $\pm$ 1.38	6.45 $\pm$ 1.11	5.98 $\pm$ 0.85	0.005*
Sig. bet. grps	$p_1=0.101$, $p_2=0.003^*$, $p_3=0.395$			

Data are presented as mean $\pm$ SD, p: p value for comparing between the studied groups, p_1 : p value for comparing between Group A and Group B, p_2 : p value for comparing between Group A and Group C, p_3 : p value for comparing between Group B and Group C, *: Statistically significant at $p \leq 0.05$.

The blood loss was more in-group B than the group A with high significant difference between the three groups ($P<0.001$). Preoperatively there was significant difference in Hb between the three groups (0.002), but postoperatively there was non-significant difference in Hb between the three groups both groups. Table 2

Table 2
The mean of blood loss in ml in studied groups

	Group A (n=20)	Group B (n=20)	Group C (n=20)	p
Blood loss	556.45 ± 70.03	854.50 ± 176.29	1111.5 ± 293.5	<0.001*
Sig. bet. grps	p ₁ <0.001*, p ₂ <0.001*, p ₃ <0.001*			
Hemoglobin (g/dl)				
Before	12.27 ± 0.41	12.72 ± 0.34	12.54 ± 0.39	0.002*
Sig. bet. grps	p ₁ =0.001*, p ₂ =0.070, p ₃ =0.296			
After	12.24 ± 0.42	12.10 ± 0.57	11.80 ± 0.88	0.099
(p ₀)	0.110	<0.001*	0.001*	

Data are presented as mean $\pm$ SD, p: p value for comparing between the studied groups, p_1 : p value for comparing between Group A and Group B, p_2 : p value for comparing between Group A and Group C, p_3 : p value for comparing between

Group B and Group C, p0: p value for Paired t-test for comparing between before and after in each group, *: Statistically significant at $p \leq 0.05$.

There was high significant difference in hospital stays between the three group ($P < 0.001$). Table 3

Table 3
The mean of operative time in both groups

	Group A (n=20)	Group B (n=20)	Group C (n=20)	p
Operative time	50.7 ± 8.31	70.5 ± 9.01	92.25 ± 7.51	<0.001*
Sig. bet. grps	p ₁ <0.001*, p ₂ <0.001*, p ₃ <0.001*			

Data are presented as mean ± SD, p: p value for comparing between the studied groups, p1: p value for comparing between Group A and Group B, p2: p value for comparing between Group A and Group C, p3: p value for comparing between Group B and Group C, *: Statistically significant at $p \leq 0.05$.

There was high significant difference in hospital stays between the three group ($P = 0.001$). Table 4

Table 4
Description of hospital stays in both groups

Hospital stay (Hours)		Group A (n=20)	Group B (n=20)	Group C (n=20)	p
After 24	No.	17	13	4	0.001*
	%	85.0	65.0	20.0	
After 36	No.	1	2	4	
	%	5.0	10.0	20.0	
After 48	No.	2	5	12	
	%	10.0	25.0	60.0	

p: p value for comparing between the studied groups, *: Statistically significant at $p \leq 0.05$

The blood transfusion of the studied cases in both groups. There was high significant difference in the blood transfusion between the three groups ($P < 0.001$). Table 5

Table 5
Description of blood transfusion of studied cases in both groups

		Group A (n=20)	Group B (n=20)	Group C (n=20)	p
Blood transfusion	No.	1	5	16	<0.001*
	%	5.0	25.0	80.0	

p: p value for comparing between the studied groups, *: Statistically significant at $p \leq 0.05$

Discussion

Uterine leiomyomas are benign tumors of the uterus, which represent the most common neoplasms in women of reproductive age and have a lifetime incidence of approximately 70% in the general population. Approximately 20-40% of women with fibroids experience significant symptoms and consult gynaecologic care [17]. Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered as a single-dose injection, either intravenously or intramuscularly [18]. In the present study we found that the blood loss was more in-group B than the group A with high significant difference between the three groups (0.001); it was in group A 556.45 ± 70.03 ml, in-group B was 854.50 ± 176.29 ml, and group C was 1111.5 ± 293.5 .

In agreement with our results, Sallam et al. [19] reported that there was high significant reduction in intraoperative blood loss in Carbetocin group (714.19 ± 186.27) compared with placebo group (1033.49 ± 140.9) ($P=0.0001$). The mean blood loss in the placebo group was 1033mL and 714 mL in the study group. This demonstrates IV Carbetocin was associated with a mean reduction in blood loss of 310 ml. Taher et al. [20] reported that the estimated intraoperative blood loss was significantly lower in the carbetocin group (436.9 ± 41.7) compared with the placebo group (621.5 ± 74.1 ; $P < .001$). The drop in postoperative hemoglobin was also significantly lower in the carbetocin group than in the placebo group at 6 and 24 hours after surgery ($P < 0.001$).

In our study we found that preoperatively there was significant difference in Hb between the three groups (0.002) as the Hb was (12.27 ± 0.424 g/dl in group A, 12.72 ± 0.336 g/dl in group B, and 12.54 ± 0.39 g/dl in group C), but postoperatively there was non-significant difference in Hb between the three groups both groups as it was lower in group B since it was (12.24 ± 0.424 g/dl in group A, 12.09 ± 0.572 g/dl in group B, and 11.80 ± 0.88 g/dl in group C). Sallam et al. [19] illustrated that there was no significant difference in related to initial hemoglobin concentration between the two groups, however there was a reduction in 24-hour post-operative hemoglobin concentration in placebo group than Carbetocin group, but this reduction does not reach the significant difference, ($P = 0.069$).

Taher et al. [20] reported that the preoperative hemoglobin level ($P=0.09$) and the percentage of adhesions did not differ between the two groups ($P=0.85$). Our findings regarding mean of operative time revealed that the operative time was (50.7 ± 8.31 in group A, 70.5 ± 9.01 in group B, 92.25 ± 7.51 in group C) there was high significant difference in operative time between the three group ($p=0.001$). Similar results were reported by Sallam et al. [19] who stated that there was a highly significant reduction in operative time in Carbetocin group ($66.35\% \pm 10.18$) compared with placebo group (95.95 ± 9.16), ($P = 0.0001$). In contrast to our results, Taher et al. [20] showed that there was no significant difference between the carbetocin and placebo groups regarding operative time ($P=0.1$) and length of hospital stay ($P=0.5$). In the current study we found that there was high significant difference in hospital stays between the studied groups (0.001).

In contrast to our results, Sallam et al. ^[19] reported that there was no significant difference between the two groups in related to their hospital stay, ($P= 0.514$). In the present study we found that the blood transfusion of the studied cases in both groups. There was high significant difference in the blood transfusion between the three groups (0.001). Matching our results, Sallam et al. ^[19] reported that the incidence of blood transfusion was increased in placebo group 30 (69.8%) patients compared with 8 (18.6%) patients in Carbetocin group, ($P=0.0001$). Helal et al. ^[21] illustrated that blood transfusion is reported to be required in up to 20% of women undergoing abdominal myomectomy. previous studies have also compared carbetocin with other uterotonic agents to lower blood loss in myomectomy. Mohamed et al. ^[17] compared 100 mg intramyometrial carbetocin injection with 400 mg rectal misoprostol and found a significantly lower intraoperative blood loss and a lower drop in hemoglobin level 48 hours postoperatively in the carbetocin group compared with the misoprostol group. Also, fewer women in the carbetocin group (four patients, 13.3%) needed blood transfusion than in the misoprostol group (eight patients, 26.7%), although this difference was not significant. Although carbetocin is more expensive than other uterotonics (e.g., oxytocin), Lawrie et al. ^[22] suggested that carbetocin might be more cost-effective than oxytocin and that the next most cost-effective option after carbetocin might be the combination of misoprostol and oxytocin for prevention of PPH at cesarean delivery. Nevertheless, the evidence was fairly uncertain and was not evaluated in the context of myomectomy.

Conclusions

The current study showed that the use of intra venous carbetocin injection during preoperative abdominal myomectomy operation is more effective in decreasing the blood loss, shorter operative time, decreasing blood transfusion and rapid postoperative recovery, than the use intramyometrial Carbetocin injection.

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Conflict of Interest: Nil

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