

Full Length Research Paper

# Efficacy of carbetocin in hemorrhage prevention during laparoscopic myomectomy

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The objective of this study was to evaluate the clinical effect and safety of carbetocin administered to prevent bleeding in laparoscopic myomectomy. A retrospective analysis of April, 2006 to April, 2011 laparoscopic myomectomy hand clinical data of 70 patients was carried out. The 70 patients were divided into treatment group and control group; the treatment group was given preoperative carbetocin, while the control group was given preoperative beta oxytocin after giving them oxytocin, which was administered in the same way as in the treatment group. Blood loss, operative time, postoperative hemoglobin (Hb) values, decrease exhaust time, and postoperative hospital stay were observed. All the patients were operated on successfully with no conversion to open surgery; 100% success rate was recorded in the treatment group as blood loss and operative time were lower in that group than in the control group, showing a significant difference ( $t = 5.31, 3.661; P < 0.05$ ). After twenty-four hours, Hb decreased in the two groups; however, the value of the difference in the decrease was not statistically significant ( $t = 2.802; P > 0.05$ ). In the treatment group, Hb value decreased after 72 h and hospital stay and discharge time after were significantly lower compared to the control group; the difference was significant ( $t = 4.902, 4.052, 4.088; P < 0.05$ ). In both groups, no serious adverse reactions and occurrence of postoperative morbidity were observed. Carbetocin showed good clinical efficacy when given to laparoscopic myomectomy patients, causing less blood loss, shorter operative time, and rapid postoperative recovery; therefore, it is safe, reliable, and worthy of clinical application.

**Key words:** Laparoscopy, myomectomy, bleeding, carbetocin.

## INTRODUCTION

Although uterine fibroids are benign and mostly common in about 20% of women over 35 years of age (Zhou et al., 2010), in recent years, its incidence in China has shown a rapid growth trend. Uterine fibroids can cause excessive menstrual flow, menstrual disorders, pelvic sense of urgency, and other symptoms. It can also be an important cause of infertility. For uterine fibroids, there is no effective drug therapy, surgery is the main treatment. The traditional surgical approach to remedying uterine fibroids has been abdominal hysterectomy or myomectomy. However, this approach brings about surgical trauma which makes postoperative recovery to be slow, especially for patients who wish to preserve reproductive function. Consequently, the traditional surgical

methods were unacceptable. With the development of minimally invasive techniques, laparoscopic myomectomy has been widely recognized and accepted by doctors and patients and it is an ideal choice, if the uterus is to be retained. However, for the majority of scholars, how to reduce the amount of intraoperative bleeding has become a major concern. Also, differences in laparoscopic myomectomy surgical procedures as well as technical proficiency of doctors in the operative field is not clear, suture or gap suture technology is not timely, and in particular, bleeding, hemostasis, and other problems occur, which will not only increase blood loss in patients with large wounds, but will also expose the clear operative field, increasing the difficulty of operation (Wu and Liu, 2009). At home and abroad the myometrium of most patients have always been injected with local oxytocin injection to promote uterine contractions and reduce bleeding, but clinical reports of the result have

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not been satisfactory (Zhaoren et al., 2009). Since there are no uniform standards for administering drugs, dose is limited to empirical treatment so as to find a safe, effective, convenient method for solving clinical bleeding problems. In recent years, researchers have explored the hemostatic effects and safety of preoperative Carbetocin in laparoscopic myomectomy patients with bleeding, as a guide to the clinical use of the drug in treatments.

## MATERIALS AND METHODS

General information was obtained from the retrospective analysis of the April, 2006 to April, 2011 laparoscopic myomectomy hand clinical data of 70 patients in our hospital. Selected patients were followed up clinically and their treatment was successfully complete. Selected patients underwent ultrasound examination cervical cytology and/or colposcopy. Patients who were diagnosed with uterine fibroids had increased volume of menstruation and had had irregular vaginal bleeding as a result of diagnostic curettage, in addition to malignant cervical lesions. Treatment was given to patients with B-Tip of the uterus such as uterine size 8 to 12 weeks pregnant and with hemoglobin 110 to 150 g/L. The seventy patients used in the study were within the age range of 25 and 45 years; their mean age was  $35.51 \pm 11.17$  years. Out of 17 cases of uterine fibroids, 13 cases had benign ovarian tumors. Selected patients (19 cases) had history of birth, gravidity 1 to 5 times the average ( $3.1 \pm 1.8$ ) times; parity 0 to 3 times the average ( $1.5 \pm 0.4$ ) times; had a caesarean section the number of parity from 0 to 1, with an average of ( $0.8 \pm 0.2$ ) times; myoma diameter  $<6$  cm 25 cases,  $6 \leq$  diameter  $<8$  cm 31 cases,  $8 \leq$  diameter  $<11$  cm 14 cases. With respect to the location of fibroids, subserosal fibroids were found in 19 cases, intramural fibroids were found in 29 cases, while submucosal fibroids were found in 22 cases. In regard to the number of fibroid, there was one in 18 cases, two or three in 30 cases, and more than three in 22 cases. The 70 patients were randomly divided into treatment and control groups, 35 patients in each group. The two sets of general information obtained from these two groups were not significantly different ( $P > 0.05$ ).

### Treatment

For a period of three to seven days after a clean surgery, the bladder of laparoscopic myomectomy patients under general anesthesia was in lithotomy position. There was routine disinfection of the devices used. A small umbilical incision was made round the lower edge of the puncture and a pneumoperitoneum was created after tube placement for laparoscopy. Patients were kept in Trendelenburg position. Left and right anterior superior iliac spine puncture was about 2 cm with a 5 mm incision on the right lower abdomen and a 10 mm incision on the left lower abdomen. Placing the operative instruments, the intestine was poked at and the uterus was moved to check the location and size of the fibroid and the presence of adhesions. For subserosal fibroids with small pedicle, a 10 mm uterine grasping forceps was used to seize the tumor and the pedicle was cut through monopolar electrocoagulation. For fibroids with thick pedicle, the myoma pedicle was ligated with the help of the Number 1 absorbable suture in order to reduce bleeding; thereafter, the fibroids were removed. For intramural fibroids which are the most prominent types of fibroids, through monopolar coagulation, a longitudinal incision was made on the surface with the incision length being slightly smaller than the diameter of fibroids and depth of the fibroids. The surgeons who were left-handed used their left hands to hold a 10 mm grasping

forceps, and grasped and stretched out the fibroids. With their right hand, they held the opposite direction of the electric knife, pushing the myometrium and leiomyoma pseudocapsule and bringing them into tight connection.

The electric knife was used to cut off the two together and this caused a separation of the fibroids from the myometrium until a point where only a small amount of the pseudocapsule was left at last. The fibroids were rotated so that the pseudocapsule of the fibroids that are turned into a bunch could also be removed by cutting them with the electric knife. If a patient had multiple fibroids, or fibroids that were far away, they were removed through an incision similar to those made for the removal of fibroids within the uterus. After myomectomy, 1 to 0 micro-uterine wound was sutured with Joe line and right iliac fossa or rectal fossa location of fibroids was dark, leaving a dead space suture layer. The lower left quadrant incision was expanded from 10 to 15 or 18 mm and the surgeon drilled into the fibroids and tumors with a nuclear crushing device removed after conventional peeling, and sent for pathological examination. Thereafter, carbon dioxide gas was released into the abdominal cavity. Also, the surface of the abdominal cavity was checked and no uterine bleeding was observed. The abdominal cavity was rinsed with normal saline, the operating instruments and trocar were removed, and the small skin incision was closed with intradermal sutures.

### Specific methods

In the treatment group, Carbetocin (trade name: clever Texin, Canada, Ferring Pharmaceutical Co., Ltd.) was given preoperatively after oxytocin (Shanghai Hefeng Pharmaceutical Co., Ltd.) had been given.

Before the fibroids in the patients were removed, a compound was formed by adding 500 ml of sodium chloride solution to a small portion of Carbetocin (100 pg); another compound was also formed by adding 500 ml of sodium chloride solution to a small portion of oxytocin (10 IU). These resulted in a reaction mixture at the end of 1 min. After adding 10 IU of oxytocin, an intravenous infusion of 85 to 100 drops was fixed at the upper right extremity for 90 min. The control group was not given preoperative beta oxytocin after receiving oxytocin which was administered in the same way as in the treatment group.

### Outcome measures

The amount of bleeding, surgery exhaustion, and hemoperitoneum pelvic fluid were calculated using volumetric method. We took the first high-hip low and tried to suck out the liquid in the chamber with special container to collect the blood. Then after the surgery, the blood was collected in a postoperative abdominal drainage bag and calculated on the basis of liquid volume.

It was observed that in the patients, the values of postoperative hemoglobin (Hb) decreased after 24 or 72 h. To review blood Hb, decreased preoperative Hb value = value - postoperative Hb value. Hospital stay time, discharge time after, operative time, etc. were also observed.

### Statistical methods

All the data obtained were measured through mean  $\pm$  standard deviation. SPSS13.0 statistical analysis software was used for data analysis. The measured data were compared using t test, while the count data were compared via  $\chi^2$  test, with  $P < 0.05$  considered as being statistically significant.

**Table 1.** The blood loss and operation time ( $\bar{x} \pm s$ ).

Group	n	Blood loss (ml)	Operation time (min)
Treatment	35	178.35	71.46
Control	35	326.34	93.29
<i>t</i>		5.131	3.661
<i>P</i>		0.000	0.002

**Table 2.** The hemoglobin value decrease, discharge time after, and length of hospital stay time ( $\bar{x} \pm s$ ).

Group	n	Hb decrease after 24 h (g/L)	Hb decrease after 72 h (g/L)	Discharge time after (h)	Length of hospital stay time (day)
Treatment	35	13.22	10.36	33.09	6.38
Control	35	13.21	18.11	47.81	9.30
<i>t</i>		2.802	4.902	4.052	4.088
<i>P</i>		0.000	0.000	0.001	0.000

## RESULTS

The blood loss, operative time, and postoperative pathology of uterine fibroids of the two groups of patients were compared. The surgery carried out on all the patients was successfully completed without conversion to open surgery, having 100% success rate. Blood loss and operative time were lower in the treatment group than in the control group; the difference was significant ( $t = 5.31, 3.661; P < 0.05$ ). These results are shown in Table 1.

Decrease in postoperative hemoglobin value, hospital stay time, and discharge time after were compared for the two groups. There was no significant difference in the decline in Hb value of the two groups after 24 h ( $t = 2.802; P > 0.05$ ); however, the Hb values of the treatment group decreased after 72 h. Hospital stay time and discharge time after were significantly lower in the treatment group compared to the control; the difference was significant ( $t = 4.902, 4.052, 4.088; P < 0.05$ ). These results are shown in Table 2.

In the treatment group, one patient had numbness in his left distal ring finger, while in the control group, one patient had headache and two patients had nausea and vomiting. These symptoms disappeared without the patients being treated consciously. The two groups had no serious adverse reactions or occurrence of post-operative morbidity.

## DISCUSSION

Uterine fibroids are the most common form of good risk tumors that affect women of childbearing age. The current treatments for uterine fibroids are many, but surgical resection is still the main treatment, including

hysterectomy and myomectomy. With hysterectomy, uterine fibroids can be completely cured, but it cannot keep women's reproductive functions. Despite the rate of relapse, myomectomy is still the most popular surgical treatment for fibroids in women. As the clinical applications and technology of laparoscopic myomec-tomy continues to improve, they bring good news to women with uterine fibroids. With the increasing popularity of laparoscopic surgery and endoscopic sur-gery, endoscopic suture techniques have been gradually recognized by everyone. However, there is the need to improve proficiency in the operation. Also, how to reduce the amount of intraoperative bleeding is still a matter of great concern for the majority of scholars. The extract or synthetic oxytocin sterile aqueous solution obtained from the oxytocin system in the posterior pituitary gland of pigs or cows is similar to the naturally occurring oxytocin of the body, which is produced by the placenta enzyme, liver, kidney, intestine and quickly removed by inactivation. *In vivo*, it has half-life of only 3 to 4 min. The onset of its action is 3 to 5 min after intramuscular injection and the duration of the action is about 30 min. However, the clinical effect of this extract is not very good (Wang et al., 2007), and as such, it is only used for empirical treatment; further research is still needed to substantiate this evidence.

Carbetocin is a synthetic long-acting oxytocin analogue. Its intravenous half-life is 40 to 50 min which is 10 times longer than that of oxytocin. That is, within 2 min after treatment of the uterine cavity with easy to use features, it has a rapid onset and long lasting action. The pharmacological effects of the posterior pituitary oxytocin release is similar to those of the non-thermal, Carbetocin and uterine oxytocin receptors in the uterus caused by rhythmic contraction, which can increase the frequency of existing contractions as well as uterine tone. The effect of

the intravenous or intramuscular injection was sustained 60 to 120 min longer than reported in a single intramuscular injection of oxytocin after the last four times. After surgery, the uterine smooth muscles were made to contract, so that the tumor protruding from the uterine surface and the level of the tumor cavity would be easy to find and peel.

During the surgical procedures, after adding a small portion of Carbetocin to the uterus, we clearly saw a white, hard, protruding tumor; this made the operation much easier. Numerous domestic and foreign studies (Dai and Shu, 2009; Xie, 2010; Chong et al., 2004) have shown that in the prevention and treatment of postpartum hemorrhage, the Cabernet oxytocin is known to have quite a good effect; a single Carbetocin injection with intravenous infusion of oxytocin will continue action for 16 h. The extended duration of Carbetocin action eliminated the need for intravenous infusion. This can partly be explained by the differences in the structure of Carbetocin and oxytocin; this structure may be related to pharmacokinetic half-life, reduced enzyme damage and difficulty to dissociate from the receptor-binding part of the drugs (Attilakos et al., 2010). In this study, in the shelling out of fibroid through laparoscopic myomectomy, a small portion of Carbetocin, in addition to oxytocin was given before the before surgery, while a simple oxytocin treatment was given after surgery to the control. Carbetocin was seen to promote uterine contraction effect more than oxytocin. Also, intraoperatively, it was seen that the myometrium was pale with strong muscle contractions; mean blood loss was significantly less in the treatment group than in the control group and there were no significant adverse reactions. The combined use of carbetocin and oxytocin in combination can significantly strengthen the uterus to contract, reducing blood loss in laparoscopic myomectomy more than oxytocin alone and as such is more effective and reliable.

An improper grasp of the surgical indications of laparoscopic myomectomy is the important cause of large blood loss. The laparoscopic myomectomy indication depends on the patient factors and surgeon's operative skills. The main factors include the type of patients with fibroids, location and size of fibroids, presence or absence of complications, and with or without fertility requirements. In general, intramural uterine fibroids and subserosal fibroids, uterine fibroids associated with clinical symptoms, are the main causes of many local compression symptoms. No matter how large a fibroid is, it can be treated through surgery. However, if a fibroid is too large (> 8 cm) or is a peri-uterine fibroid in the lower section of the uterine artery wall, it could still be removed easily through minimally invasive surgery which is more dependent on the surgeon's skills, but this will lead to prolonged suture difficulties and significant increase in blood loss (Agostini et al., 2005). In this study, 19 patients had fibroids > 8 cm in the treatment group. After surgery, one patient out of all the surgical patients in the group

had bleeding using suture needle; no improvement was observed after 10 min, but when oxytocin added, there was a good clinical response. In the other group, one patient who had multiple uterine fibroids had a very large volume of intraoperative blood loss and packed red blood cells, and as such, was given 4 u infusion, in addition to oxytocin. Thus, the bleeding was brought under control.

In summary, giving Carbetocin preoperatively to laparoscopic myomectomy patients had good clinical efficacy, bringing about less blood loss, shorter operative time and rapid postoperative recovery. It is, therefore considered safe and reliable and worthy of clinical applications.

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