Original Article
A comparative study on two pituitrin injection methods in laparoscopic salpingotomy for tubal pregnancy

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Abstract: Background: Tubal pregnancy is a common gynecological acute abdomen, and is often treated by laparoscopic salpingotomy. This study aimed to compare two pituitrin injection methods in laparoscopic salpingotomy for tubal pregnancy. Methods: 200 patients with unruptured tubal pregnancy were randomly divided into observation group 1, observation group 2 and control group. Before laparoscopic salpingotomy, the patients in observation group 1 and 2 were injected with pituitrin at corpus uteri and mesosalpinx, respectively. The control group did not use pituitrin injection. The intraoperative and postoperative conditions and postoperative tubal patency and pregnancy among three groups were compared. Results: The intraoperative blood losses in observation groups 1 and 2 were significantly less than control group (P < 0.05), and the operation durations in observation groups 1 and 2 were significantly shorter than control group (P < 0.05). The postoperative persistent ectopic pregnancy rates in observation groups 1 and 2 were significantly lower than control group (P < 0.05). After operation, the tubal patency rates and intrauterine pregnancy rates in observation group 1 and observation group 2 were significant higher than control group (P < 0.05), and the recurrent ectopic pregnancy rates in observation groups 1 and 2 were significantly lower than control group (P < 0.01). There was no significant difference of above indexes between two observation groups (P > 0.05). Conclusions: For patients with tubal pregnancy, both injection of pituitrin at corpus uteri and mesosalpinx during laparoscopic salpingotomy can reduce the blood loss and operation duration, and improve the tubal patency and intrauterine pregnancy rates.

Keywords: Laparoscopy, tubal pregnancy, pituitrin, salpingotomy

Introduction

Ectopic pregnancy is a common gynecological acute abdomen. Its incidence is about 2% of the total number of pregnancy, and there is a clear increasing trend year by year. 95% of ectopic pregnancy cases are with tubal pregnancy [1, 2]. With the improvement of patient awareness, wide application of serum β-human chorionic gonadotropin (HCG) detection technology and development of ultrasound diagnostic technology, the diagnosis and treatment levels of ectopic pregnancy also increase, and the vast majority of ectopic pregnancy can be diagnosed early [3].

The ipsilateral salpingectomy has been used for the usual surgical treatment of tubal pregnancy. Although in short term the surgical approach does not affect ovarian volume, it can influence on the ipsilateral ovarian reserve function, blood supply and superovulation [4]. Therefore, some scholars believe that, in clinic the tubal pregnancy patients with later fertility requirements should select conservative surgery to retain affected tubal, and salpingotomy is one of the most common procedures. However, compared with salpingectomy, the wound bleeding caused by salpingotomy is difficult to treat, and there may be a postoperative persistent ectopic pregnancy risk [5]. It is well know that, with the extensive development, the laparoscopic techniques have advantages such as less trauma and faster recovery, so un-ruptured tubal pregnancy is more likely to select this treatment. Some clinical studies confirm that, the laparoscopic surgery can protect the postoperative reproductive status of fallopian tube for tubal pregnancy patients with no adverse medical history or tubal adhesions [6]. The active fluff can erode the tubal muscularis

with rich blood vessels, and after incision the oviduct is likely to bleed at the blastocyst attachment site. In surgery, the local coagulation is often used to stop bleeding, but the electric coagulation on tubal wound will affect the postoperative tubal repair function [7, 8]. Therefore, if the wound bleeding can be reduced, there will be a clear operative field, and an improvement of the coagulation accuracy and reductions of coagulation times and coagulation durations can reduce the application of coagulation during surgery and improve tubal functional recovery and the effect of surgery. This it is very important for protection of the tubal reproductive state.

Pituitrin can constrict the blood vessels, and reduce the blood flow. It has been used for gynecologic surgery since 1950s, and now there is a wide range of applications such as myomectomy surgery and gynecological surgery [9]. Some literatures [10, 11] report that, after laparoscopic salpingotomy, the injection of pituitrin in the corresponding mesosalpinx can shorten the operation time, stop the bleeding, and reduce the need of coagulation, so the adverse impacts of the fallopian tubes resulted by the coagulation and the extend operation time can be reduced. However, the improper operation of mesosalpinx injection is easy to cause mesangial hematoma, tubal ischemia, necrosis, or delayed bleeding [9]. The tubal blood supply originates from the branches of ovarian artery which spread in mesosalpinx, and the branches of uterine artery at the uterine horn [12, 13]. It is deduced that, injection of pituitrin at corpus uteri can promote the vasoconstriction at uterine horn, and reduce the blood flow of mesosalpinx and wound bleeding in surgery. This method is not only easy, but also can reduce the problems brought by the mesosalpinx injection. This study compared the intraoperative blood loss, operation duration, postoperative tubal patency and intrauterine pregnancy between pituitrin injection at corpus uteri and ipsilateral mesosalpinx in laparoscopic salpingotomy for treating tubal pregnancy. The objective was to provide a basis for further application of pituitrin injection at corpus uteri to laparoscopic salpingotomy.

Materials and methods

Subjects

Two hundred patients with ectopic pregnancy in First Affiliated Hospital of Sun Yat-sen University from December 2006 to December 2010 were enrolled in this study. They were diagnosed by histological and gynecological examination, pelvic ultrasound and serum β-HCG detection, and were confirmed with unruptured tubal pregnancy via laparoscopy. The inclusion criteria were as follows: the patients had fertility aspiration and requirement of keeping the oviducts; they had no cervical, ovarian or abdominal pregnancy; the preoperative serum β-HCG detection and ultrasound prompted that the pregnancy mass size did not affect the choice of surgical approach. The exclusion criteria were as follows: shock manifestation; acute pelvic and abdominal infection; tubal stiff distortions in affected side; systemic disease affecting the laparoscopic surgery; blood diseases and coagulation disorders. The age of 200 patients was 18-37 years (average 26.8± 4.0 years). The preoperative pregnancies were 0-6 times (average 1.5±1.6 times). The time of menstruation cessation was 37-81 days (average 48.5±9.1 days). The abdominal pain continued for 0-30 days (average 4.5±6.7 days). The median level of serum β-HCG was 1262-8400 IU/L (average 2536±428.7 IU/L). The amount of intra-abdominal hemorrhage was 30-300 ml (average 110±63.5 ml). 12 patients had history of lower abdominal surgery (cesarean section, appendicitis surgery); 27 cases were placed with the intrauterine device (IUD). This study was approved by the Ethics Committee of First Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all participants.

Grouping

The patients were randomly divided into three groups (observation group 1, observation group 2 and control group). In observation group 1 (72 cases), after confirmation of tubal pregnancy by laparoscopy, the patients were injected with pituitrin hormone in corpus uteri for laparoscopic salpingotomy. In observation group 2 (62 cases), the patients were injected with pituitrin at the ipsilateral mesosalpinx. In control group (66 cases), the patients were not injected with pituitrin.

Surgical procedure

All patients underwent the laparoscopic salpingotomy. All operations were completed by the gynecologist with experience > 5 years. The patients were performed with tracheal intuba-

Table 1. General information of patients in three groups

Index	Group		
	Observation 1 (n=72)	Observation 2 (n=62)	Control (n=66)
Age (year)	26.3±4.1	27.2±3.8	27.5±3.9
Nullipara (n, %)	40 (55.6%)	34 (54.84%)	36 (54.5%)
Menstruation cessation (day)	45.9±5.2	46.3±5.0	46.1±4.8
Abdominal pain (n, %)	3.5±3.2	3.6±3.3	3.7±3.0
Vaginal bleeding (day)	5.6±4.5	5.5±4.4	5.3±4.2
Abdominal surgery history (n, %)	21 (29.2%)	18 (29.0%)	19 (28.8%)
IUD using (n, %)	10 (13.9%)	8 (12.9%)	9 (13.6%)
β-HCG (mIU/L)	2466.3±431.5	2553.3±471.5	2342.5±412.6
Adnexal mass diameter (cm)	3.6±2.5	3.8±2.4	4.1±2.3

IUD, intrauterine device; β-HCG, β-human chorionic gonadotropin.

tion and inhalated general anesthesia. The intraoperative arterial CO_2 partial pressure and O_2 saturation were monitored. The patients were in the lithotomy position. After abdominal and perineal skin disinfection, a 16th double-lumen catheter was inserted. The umbilical puncture injection of CO_2 gas was carried out to establish the pneumoperitoneum. A 10 mm laparoscope was placed, and a 5 mm puncture cannula was placed on both sides of the lower abdomen to place the surgical instruments. The abdominal and pelvi cavity, uterine, tubal and ovarian morphology were observed, and the tubal pregnancy was confirmed. In observation group 1, a long needle was placed from the affected side of abdominal wall into the abdominal cavity, and was linked with the abdominal external syringe for injection of 20 ml pituitrin (diluted with normal saline to a concentration of 0.5%) in corpus uteri. In observation group 2, 20 ml of 0.5% pituitrin was injected in the less-vessel area of mesosalpinx in affected side. In control group, no pituitrin was injected.

The embryonic site of tubal pregnancy was longitudinally incised, and the embryo and blood clots was found to form a tissue block with complete pseudocapsule. After washing out the outer edge of pseudocapsule, the tissue block was striped out completely and removed from the abdominal cavity. The electric coagulation was performed for stanching bleeding at tubal resection margin and preventing intraluminal active bleeding. The tubal longitudinal incision was sutured by 2/0 absorbable suture to obtain the normal morphology. The adhesiolysis was conducted for patients with loose adhesion in the pelvic cavity, and the intra-abdominal hemorrhage was cleared.

Observation indexes

The operation duration in each group was recorded from the first incision beginning to the suture of last incision. The intraoperative blood loss was estimated by commonly used method (measuring gauze weight and bleeding amount in negative pressure bottle). The maximum body temperature from the day of operation completion to discharge was recorded. The β-HCG level was measured once every two days after surgery. The postoperative anti-infection treatment was performed for pelvic inflammatory disease during operation. The postoperative contraception was implemented. After 3-7 days from menstruation cessation after postoperative 3 months, the patients received hysterosalpingography for ascertaining the affected tubal patency [14, 15]. The patients were guided for early planed pregnancy to improve the opportunity of intrauterine pregnancy [16]. If the postoperative serum β-HCG level did not decline or rise again after declining, the patients were diagnosed with persistent ectopic pregnancy. If the disease condition was stable, 50 mg methotrexate was given via intramuscular injection. The serum β-HCG level was observed continuously until it dropped to normal. If the postoperative pregnancy in oviduct, ovary or abdominal cavity occurred, the patients were diagnosed with recurrent ectopic pregnancy.

Statistical analysis

All statistical analysis was carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as number with percentage or mean ± SD. Comparisons among three groups were performed by multi-group

Table 2. Distributions of tubal pregnancy location and type in three groups

Index	Group		
	Observation 1 (n=72)	Observation 2 (n=62)	Control (n=66)
Location (n, %)			
Ampullar	46 (63.9%)	40 (64.5%)	42 (63.6%)
Isthmus	19 (26.4%)	16 (25.8%)	17 (25.8%)
Fimbria	5 (6.9%)	4 (6.5%)	5 (7.6%)
Interstitial	2 (2.8%)	2 (3.2%)	2 (3.0%)
Type (n, %)			
Pregnancy	66 (91.67%)	57 (91.94%)	61 (92.42%)
Abortion	6 (8.33%)	5 (8.06%)	5 (7.58%)

Table 3. Interoperative conditions of patients in three groups

Index	Group		
	Observation 1 (n=72)	Observation 2 (n=62)	Control (n=66)
Intraoperative			
Blood loss (ml)	46.2±23.7[a]	42.4±28.5[a]	74.3±33.7
Operation duration (min)	45.1±14.2[a]	47.9±20.1[a]	77.6±29.5
Postoperative			
Body temperature (°C)	5.2±2.3	4.9±2.7	5.8±3.1
Hospital stay (day)	37.8±0.8	37.8±0.8	37.8±0.8
PEP (n, %)	1 (1.4%)[a]	1 (1.6%)[a]	3 (4.5%)

[a]P < 0.05 compared with control group; PEP, persistent ectopic pregnancy.

variance analysis. If there were differences, the differences between two groups were analyzed by one-way ANOVA or t-test, and comparison of rate was analyzed by χ^2 test. P < 0.05 was considered as statistically significant.

Results

General information of patients

The general information including patient age, number of nullipara patient, time of menstruation cessation, time of vaginal bleeding, abdominal surgery history, number of patients using IUD, serum β-HCG level and adnexal mass diameter by B-ultrasound were showed in **Table 1**. There was no significant difference of these indexes among three groups (P > 0.05).

Total operation outcomes and distributions of tubal pregnancy location and type

All patients in three groups were diagnosed as tubal pregnancy via laparoscopy, and were smoothly treated with laparoscopic salpingotomy. No case needed salpingectomy due to operation difficulty, intraoperative or postoperative bleeding or failure in conservative treatment of persistent ectopic pregnancy, and no case needed laparotomy. The distributions of tubal pregnancy location and type in three groups were shown in **Table 2**, and there was no significant difference among three groups (P > 0.05).

Intraoperative and postoperative conditions of patients in three groups

The intraoperative blood loss, operative duration, postoperative body temperature, duration of hospital stay, and incidence of PEP in three groups were shown in **Table 3**. The intraoperative blood losses in observation group 1 and 2 was 46.2±23.7 ml and 42.4±28.5 ml, respectively, which were significantly less than 74.3±33.7 ml in control group (P < 0.05). The operation durations in observation group 1 and 2 were 45.1±14.2 min and 47.9±20.1 min, respectively, which were significantly shorter than 77.6±29.5 min in control group (P < 0.05). There was no significant difference of intraoperative blood loss or operation duration between two observation groups (P > 0.05).

The postoperative body temperature had no significant difference among three groups (P > 0.05). The durations of hospital stay in observation group 1, observation group 2 and control group were 5.2±2.3 days, 4.9±2.7 days and 5.8±3.1 days, respectively, with no significant difference among them (P > 0.05). The persistent ectopic pregnancy rates in observation group 1 and observation group 2 were 1.4% and 1.6% respectively, which were significantly lower than 4.5% in control group (P < 0.01), and there was no significant difference between 2 observation groups (P > 0.05). 5 cases with persistent ectopic pregnancy received postoperative methotrexate treatment until discharging when the serum β-HCG level decreased to 50% of the preoperative level. No second operation was performed.

Table 4. Postoperative tubal patency and pregnancy in three groups

Index	Group		
	Observation 1 (n=72)	Observation 2 (n=62)	Control (n=66)
Tubal patency (n, %)	52 (72.22%)[a]	40 (64.52%)[a]	34 (51.51%)
Intrauterine pregnancy (n, %)	49 (67.24%)[a]	41 (53.66%)[a]	32 (48.84%)
Recurrent ectopic pregnancy (n, %)	9 (12.5%)	8 (12.9%)	15 (22.72%)

[a]P < 0.05 compared with control group; REP, recurrent ectopic pregnancy.

Postoperative tubal patency and pregnancy

The patients in three groups were followed up for more than 18 months (average 20.1±4.2 months). Hysterosalpingography was performed in all patients within 3-7 days after menstruation cessation from postoperative 3 months. As shown in **Table 4**, the results suggested that, there were 52, 40 and 34 cases of tubal patency in observation group 1, observation group 2 and control group, respectively. The tubal patency rates in observation group 1 (72.22%) and observation group 2 (64.52%) were significant higher than that of the control group (51.51%) (P < 0.05), while there was no significant difference between two observation groups (P > 0.05).

There were 49, 41 and 32 cases of intrauterine pregnancy in observation group 1, observation group 2 and control group, respectively, with rates of 68.1%, 66.1% and 48.5%, respectively. There were 9, 8 and 15 cases of recurrent ectopic pregnancy in observation group 1, observation group 2 and control group, respectively, with rates of 12.5%, 12.9% and 22.72%, respectively. The intrauterine pregnancy rates in observation group 1 and observation group 2 were significantly higher than control group (P < 0.05), and there was no significant difference between two observation groups (P > 0.05). On the contrary, the recurrent ectopic pregnancy rates in observation group 1 and observation group 2 were significantly lower than control group (P < 0.01), with no significant difference between two observation groups (P > 0.05).

Discussion

Ectopic pregnancy is a common gynecological acute abdomen, the delayed diagnosis and treatment can jeopardize the patient's health and life, and its incidence has appeared a rising trend in recent years [1, 2]. Laparoscopic surgery with less trauma, quick recovery and diagnostic value has became the first choice for the diagnosis and treatment of ectopic pregnancy, especially for childless women and young female with the requirements of fertility or the tubal function keeping, it has became an important treatment of tubal pregnancy. Salpingotomy, one of the most widely used conservative surgeries, can not only retain the fallopian tube and fix the morphology of the fallopian tube, but also protect the traffic in blood supply between the fallopian tubes and ovaries, and avoid salpingectomy [4, 17].

Some literatures [14, 17, 18] have reported that, the relevant factors of the laparoscopic salpingectomy include preoperative serum β-HCG levels, ectopic pregnancy mass size, preoperative hemoperitoneum and fetal survival judged by B-ultrasound. Serum β-HCG level is the most important factor. The cause may be related to the tubal muscularis erosion of fluff, which develops with blastocyst growth. In tubal pregnancy, the higher level of serum β-HCG, the deeper planting depth of the fluff in the fallopian tube. This leads to the bleeding of attachment site after ipsilateral tubal incision and removal of embryo, affecting the operative field. So the repeated surgical grab of tubal muscularis aggravates the damage of the fallopian tubes, and the bleeding is often stopped by local coagulation. More blood loss brings more times or longer coagulation, thus the surgery will fail, and the tubal damage cannot be repaired; the local adhesions, blocks and partial missing will form. It is consistent with the experiences about treatment in our clinical work. It is reported that for tubal pregnancy patients with no adverse medical history and tubal adhesions, laparoscopic surgery is conducive to the postoperative tubal reproductive status [6], but in laparoscopic surgical procedures, an increased times and longer duration of coagulation can lead to thermal damage and destruction of the oviduct and myometrium, and affect postoperative tubal repair and oviduct function [7, 8]. Therefore, a reduced intraoperative tubal coagulation is very important for tubal reproductive status, and the intraoperative bleeding of the tubal pregnancy is one

of the direct causes of tubal wound coagulation. In order to alleviate tubal damage and protect the reproductive status of fallopian tubes, the reduction of intraoperative tubal wound bleeding, maintaining of a clear vision, increased hemostasis accuracy and reduction of the hemostasis frequency and duration are needed.

Pituitrin has been widely used in laparoscopic uterine fibroids stripping surgery; it constricts blood vessels, and reduces blood flow. Stock et al [10] found that, after the conservative laparotomy for tubal pregnancy, injection of diluted pituitrin into mesosalpinx could obtain a good hemostatic effect. In the laparoscopic salpingotomy, Ugur et al [11] injected diluted pituitrin into mesosalpinx and found that, injection of pituitrin could obtain significant shorter operative duration and coagulation time compared no using pituitrin. This indicates that, the injection of pituitrin in mesosalpinx during salpingotomy can reduce operative duration, coagulation times and the bad effort of repeated grabs of fallopian tubes. Other scholars [19, 20] use a large number of diluted pituitrin in surgical treatment of interstitial pregnancy and believe that, this method is safer, more effective, with less bleeding and lower complication, compared with uterine horn ministry resection, and can retain the reproductive function. This study confirms that, the applications of pituitrin at mesosalpinx and uterine body are effective for hemostasis in salpingotomy. The two methods can not only reduce the amount of bleeding but also create a clear endoscopic operative field. The reduction of tubal coagulation can shorten the duration of surgery. However, in our clinical experience, the injection of diluted pituitrin in mesosalpinx may increase the damage of the fallopian tubes, impact operative visual field caused by the thickening and swelling of mesosalpinx. The incision wound is not apt to linear or need multiple cuts. After removal of the embryo, the tubal mucosa and muscularis are hard to match neatly. The corpus uteri injection of pituitrin can reduce the tubal damage brought by local operation, but does not affect the appearance of the fallopian tube. It is more conducive to incision suture. The more important is that this method is easier to operate.

Previous studies [1, 21-23] found that, after laparoscopic conservative surgical treatment of tubal pregnancy, the persistent ectopic pregnancy rate was 4%-5%, and the incidence of recurrent ectopic pregnancy was about 15.4%-24.1%. In this study, the persistent ectopic pregnancy and recurrent ectopic pregnancy rates of control group were 4.5% and 22.72%, roughly equal to the above reports. The persistent ectopic pregnancy rates in observation group 1 and 2 were 1.4% and 1.6%, respectively, and the recurrent ectopic pregnancy rates were 12.5% and 12.9%, respectively, which were significantly lower than control group.

Currently, laparoscopic hydrotubation is the gold standard for the evaluation of tubal patency, but it is an invasive surgery, so hysterosalpingography is still the non-invasive method and surgical evaluation of tubal patency effects [13, 14]. It is believed that patients with tubal ectopic pregnancy have no natural pregnancy after surgery 12-18 months should seek assisted reproductive technology [24]. This can be explained that, the postoperative intrauterine pregnancy mainly concentrates in less than 2 years, and the best time is 6 months. Therefore, the postoperative follow-up time is more than 18 months. In this study, the tubal patency and intrauterine pregnancy rates in the observation groups were higher than control group, and the persistent ectopic pregnancy and recurrent ectopic pregnancy rates were lower than control group. This may be due to the reduction of opportunities of tubal coagulation during the surgery and a better protection of the affected tubal reproductive function.

Due to the side effect of elevating the blood pressure, pituitrin is forbidden for patients with coronary artery disease, hypertension, heart failure or pulmonary heart disease. It is also reported that, pituitrin in gynecological surgery may be the factor of tubal necrosis, delayed bleeding, cardiac arrest and other serious complications [9]. In this study, two observation groups were with stable blood pressure and had no case with abnormal elevation, bradycardia or delayed bleeding adverse event. Therefore, during the injection process of pituitrin, the indications should be strictly controlled. The repeated withdrawing of blood can avoid the direct injection of pituitrin into the blood vessel which causes serious complications. In addition, a timely communication with the ane-

sthesiologist and serious monitoring are needed to ensure patient safety.

In conclusion, for patients with tubal pregnancy, both injection of pituitrin at corpus uteri and mesosalpinx during laparoscopic salpingotomy can reduce the blood loss and operation duration, and improve the tubal patency and intrauterine pregnancy rates. However, the corpus uteri injection is more convenient, simpler and quicker than mesosalpinx injection. It can not only reduce the damage to fallopian tubes, conducive to the fallopian tubes suture repair, but also reduce the blood loss and opportunity of tubal coagulation and shorten the operation time. The sample size in this study is relatively small, and the observation time is short. In addition, the patients are with stable unruptured ectopic pregnancy. The postoperative tubal patency and intrauterine pregnancy of different pituitrin applications in laparoscopic salpingotomy also require large-sample clinical data and long-term follow-up for further investigation.

Disclosure of conflict of interest

None.

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