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Review article

Laparoscopic uterine artery occlusion for the treatment of symptomatic uterine fibroids

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ABSTRACT

With the development of gynecologic laparoscopy technology in recent years, uterine artery occlusion by laparoscopy (UAOL) has become a primary treatment for symptomatic uterine fibroids. Uterine artery occlusion by laparoscopy to treat uterine fibroids has favorable clinical outcomes such as relieving menometrorrhagia, decreasing uterine volume, and reducing the recurrence rate of fibroids. However, the therapeutic mechanism of UAOL remains unclear. It may be that the mechanism of UAOL is mostly associated with the uterine blood supply and uterine intramural arterial paths and with the difference between the uterine myometrium and fibroid tissues in the coagulation–fibrinolysis system. Therefore, this study reviewed and generalized many documents on the clinical effects and therapeutic mechanism of UAOL.

Introduction

Uterine leiomyoma is the main cause of hysterectomy in women of reproductive age. American data show that every year nearly 200,000 women undergo a hysterectomy because of uterine fibroids. However, there is no related epidemiological data in China. Dr. Victor Bonney is a gynecological operation expert and once said that “For uterine fibroid hysterectomy is undoubtedly a rather excision surgery failed completely” (Bonney Gynaecological Surgery, 10th Edition). An increasing number of doctors and patients are concerned about the physiological function of the uterus and preserving the organ's integrity. Scholars have reviewed operation modes. A variety of uterus-preserving treatment methods have been developed. The outcome of laparoscopic uterine artery occlusion as the primary treatment used in the management of uterine fibroids is satisfactory. We searched the literature in the English language using the keywords ‘laparoscopy’, ‘uterine fibroids’, “uterine artery occlusion”, “leiomyoma”, and “therapeutic” in the PubMed database. We therefore performed a review on the clinical application of this technology in recent years and the therapeutic mechanisms.

Background of the development of the technology

In 1995, the French physician Jacques Ravina[1] and team first reported using uterine artery occlusion by embolization (UAOE) to treat symptomatic uterine fibroids. At first they only treated patients who were going to undergo myomectomy before the operation. The amount of intra- and postoperative hemorrhages was significantly reduced. At the same time, the treatment was good for rescuing hemorrhages due to uterine leiomyomas, relieving menorrhagia symptoms, and reducing the uterine volume significantly. Encouraged by the results of this study, Ravina's team began to apply UAOE in the treatment of uterine fibroids. They chose 16 patients with uterine fibroids who were older than 35 years and did not have fertility requirements as the object for UAOE. The success rate of surgical treatment was 87.5% and the volume of the tumor was reduced by 36%. Since 1995, doctors from many countries have successfully applied this method to treat uterine fibroids with a satisfactory outcome.

Uterine artery occlusion (UAO) created a new approach for the treatment of uterine fibroids. Since the advent of UAOE, doctors

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began trying to ligate the uterine artery in laparoscopy,[2] and obtained a satisfactory short-term clinical effect. In 2000, Liu[3] first reported blocking the bilateral uterine artery by using a laparoscopic bipolar coagulation technique to treat three cases of symptomatic uterine myoma. The follow up during 6 months showed that the relief rate of abnormal menstruation was 100%, the uterine volume reduced by 36~42%, and the prominent myoma shrank to 73–79%.

The application of UAO in the treatment of gynecologic hemorrhage diseases has many years of history, although few gynecologists are aware of the important status of UAO in the treatment of uterine fibroids.[2] A clinical study shows UAO has significant clinical effects and the advantage of allowing a minimally invasive approach for patients with a uterine leiomyoma. Uterine artery occlusion by laparoscopy (UAOL) combined with electrocoagulation technology is gradually replacing the traditional mode of treating uterine fibroids. In addition, UAOL avoids ovarian radiation injury and accidental embolism in the ovarian artery. It is usually unnecessary for UAOL to depend on the radiologist' assistance. UAOE has often more time consuming, higher cost and the complications associated with embolism syndrome. Uterine artery occlusion by laparoscopy has more advantages, and gynecological doctors and patients are increasingly accepting it.

The characteristics and clinical curative effect of UAOL

We usually choose to block the initial portion of the uterine artery because its anatomical landmarks are easy to identify. However, it is unclear whether there is a difference between occluding the trunk of the uterine artery and occluding it near the uterus. Uterine artery occlusion by laparoscopy is usually performed under general anesthesia, and the surgeon requires a great amount of experience in endoscopic surgery.

In general, to open the peritoneum and search for the uterine artery, we choose the triangle surrounded by the round ligament of the uterus, the infundibulopelvic ligament, and the external iliac vessels. The uterine artery usually begins from the anterior branch of internal iliac artery and has a diameter of approximately 2–6 mm and tortuous shape. The rhythmical pulse from the uterine artery can be observed clearly under laparoscopic vision. The ureter goes underneath the uterine artery at a paracervical distance of 2 cm. Bipolar electric coagulation or plasma knife (PK) were used to block uterine artery. The power was controlled between 40–45 W, and the band width of coagulation was required for 1–1.5 cm.[4] The traffic branches of the uterus ovarian artery can provide abundant compensatory blood supply to the uterus; therefore, the traffic branches should be blocked simultaneously for patients who have no fertility requirements. When dissecting and coagulating the uterine artery, physicians should be sufficiently careful to avoid damaging the basin wall, iliac vessels, and bilateral ureters.

In 2001, Liu[5] treated 87 patients with uterine leiomyoma by UAOL; the success rate of the operation was 97.7% (85/87 patients), the mean follow-up time was 10.2 months, the symptom relief rate was 89.4%, the uterine volume reduced by 46%, and the dominant myoma shrank by 76%. Liu's[5] study also found that the size of dominant fibroids with a diameter of $\geq$ 5 cm shrank more remarkably (86%). Yen[6] treated 46 patients with leiomyomas by using laparoscopic uterine artery and uterus ovarian artery occlusion therapy. The patients' postoperative follow up lasted 6 months. The relief rate of excessive menstruation, dysmenorrhea, and oppressive symptoms was 71.7%, 56.5%, and 38.7%, respectively. The volume of the uterus and leiomyoma was reduced by 38.3% and 59.1%, respectively. Mara et al[7] retrospectively analyzed 100 patients who had uterine fibroids and received UAOL treatment. The patients were followed up for 6 months. Mara et al[7] found that the volume of the leiomyomas was reduced by 39%. Helal et al[8] treated 45 patients with leiomyomas by using UAOL; they were then followed up for 1 month, 3 months, 6 months, and 12 months. The abnormal menstruation relief rate reached 86.7%, on average. To sum up, the clinical outcomes are satisfactory for UAOL technology in the treatment of uterine fibroids.

In 2000, Dr. Zhongping Cheng[9] and team from China performed the UAOL procedure, and designed an operation method in which uterine artery occlusion by laparoscopy is combined with myomectomy (UAOL-M) for patients with symptomatic uterine leiomyomas. Cheng found that UAOL-M ($n = 348$) has a better clinical effect than laparoscopic myomectomy (LM; $n = 172$). Clinical outcomes were compared between the two groups: the postoperative morbidity (24 hours after operation, 2 days, 6–8-hour intervals, consecutive body temperature > 38.0°C for 2 times) was lower in the UAOL-M group than in the LM group (5.7% vs. 19.2%, respectively; $p < 0.001$); the uterine volume reduction was more remarkable in the UAOL-M group than in the LM group (48.9% vs. 39.3%, respectively; $p < 0.05$); the remission rate of menorrhagia was increased in the UAOL-M group than in the LM group (97% vs. 86.4%, respectively; $p < 0.001$); and the postoperative recurrence rate of leiomyoma was significantly reduced in the UAOL-M group than in the LM group (3.0% vs. 10.7%, after an average follow up of 28.2 months; $p = 0.001$). No uterine necrosis or rupture occurred in the UAOL-M group. The improved effects in the UAOL-M group are associated with the following factors. First, intraoperative bleeding was significantly reduced in the UAOL-M group because of the UAOL procedure; therefore, the process of hemostasis by electric coagulation was decreased. Fewer eschars grew and were absorbed by the surrounding tissues. As a consequence, postoperative fever and postoperative morbidity were lower in the UAOL-M group than in the LM group. Second, a leiomyoma originates from a unicellular growth in a single smooth muscle cell that clones and proliferates. The nucleus of the fibroid cell can be very small, and 77–80% patients have multiple leiomyomas. It is difficult to remove fibroids completely by LM. Remnants of leiomyomas increase the risk of recurrence. After performing UAOL, the growth of residual small fibroids may be stopped because of hypoxia, and the recurrence rate of fibroids would be reduced. Third, because of UAO, the primary purpose of suturing the uterine wall is more to recover the uterine shape and anatomic position than to achieve hemostasis. Therefore, the degree of difficulty of stitching is reduced and the operation of suturing is simplified. By contrast, the visual field under laparoscopy is much clearer because of reduced bleeding, which aids the endoscopic doctor in performing complicated operations such as a difficult myomectomy of a myoma in the broad ligament or in a cervical position or the removal of multiple myomas. Therefore, the indication for LM was expanded.[10,11]

The treatment mechanism of UAO

The clinical effect of UAO in the treatment of uterine fibroids is satisfactory, although the mechanism of the treatment remains unclear. The clinical outcomes in which the leiomyoma dies but the uterus survives may be associated with the following three factors.

The characteristics of the uterine blood supply

First, the sources of the uterine blood supply and the characteristics of blood flow paths should be known. The blood supply of the uterus is very rich and primarily comes from the bilateral uterine artery, which has a diameter of 2–6 mm. The second supply is the uterine ovarian artery, which has a diameter of 0.5 mm. In addition, many named arteries are also included: inferior mesenteric artery, lumbar artery, spinal artery, median sacral artery, deep

iliac circumflex artery, inferior epigastric artery, circumflex femoral artery, and the medial and lateral branches of the circumflex femoral artery. Many unnamed arteries that go through the broad ligament and retroperitoneum can also supply blood. The blood flow paths inside the uterus are also very rich. The left and right sides of the arcuate arteries are connected to each other in the middle part of the walls of the uterus. The branches of the arcuate artery also anastomose at the side wall of the uterus.

The uterine blood supply provides a powerful guarantee for the reperfusion and recovery of the uterus after arterial blocking. After UAO, uterine muscle recovery primarily depends on perfusion by a rich blood supply. The second factor contributing to uterine muscle recovery is related to the anatomical characteristics of artery inside the uterus. However, in a leiomyoma, there is no reperfusion of blood flow. Studies using magnetic resonance imaging (MRI) technology have found that the myometrium and leiomyoma will undergo ischemia immediately after UAOE. The muscular layer of the uterus was reperfused after 7 days, but the leiomyoma tissue was not reperfused. Brophy et al[12] analyzed MRI images for uterine blood flow in 32 patients with leiomyomas who underwent UAOE. The images were obtained before the operation and at 24 hours, 3 months, and 6 months after the operation. The blood flow was reduced at 24 hours after the operation; however, it soon recovered to the normal level. The level of blood perfusion in leiomyoma tissues continuously declined over the three time points. In a study by Lichtinger et al,[13] an electrode catheter (which can detect the pH value) was embedded in the endometrium or myometrium of 13 patients with uterine fibroids. The pH value dropped to the lowest point 36 minutes after UAO, on average. After 2 hours, 4 hours, 6 hours, and 8 hours, the pH values returned to approximately 46% of the normal level, 70% of the normal level, 80% of the normal level, and 95% of the normal level, respectively. It is generally believed that the changes in the pH value are in response to the level of hypoxia in uterus after uterine artery blockage; 80% of the uterine blood supply will recover within 6 hours after UAO.

The difference in coagulation–fibrinolytic system

Because of the occlusion of the uterine artery, ischemic changes due to reduced blood flow and blood clotting occurs in the smooth muscle and in the leiomyoma. The uterus then regains reperfusion, but the leiomyoma is unable to regain a blood supply. Some scholars speculate that differences in the coagulation–fibrinolytic system must exist between the muscular layer and a leiomyoma.[14] Computed tomography (CT) and MRI technology reports show thrombus dissolution in myometrial vessels but not in leiomyomas.[14] Computed tomography imaging shows that thrombolysis occurs 6–24 hours after UAO in the myometrium. However, neither thrombolysis nor reperfusion occurs in fibroids.[14] A MRI examination also shows the same results. After the UAO operation, MRI images of uterine blood flow at 1–4 days, 1 week, 1 month, 2 months, 3 months, 4 months, 6 months, and 12 months show that the perfusion of the uterus was significantly decreased on the 1st day after the operation; it then recovered to 44% of the normal value on the first 1–4 days; perfusion significantly improved after 1 week, and recovered to normal after 1 month, 2 months, 3 months, 4 months, 6 months, and 12 months. However, the leiomyoma had no reperfusion, even at 1 year after the operation. On researching the plasminogen activator and plasminogen activator inhibitor (PA/PAI) system in the leiomyoma and smooth muscle tissue, Cheng et al[15] found that the gene and protein level of urokinase plasminogen activator (i.e., t-PA) were lower in leiomyoma tissue than in smooth muscle tissue ($p < 0.05$). Type I PA inhibitor (PAI-1) was significantly higher in leiomyoma tissue than in smooth muscle tissue ($p < 0.05$). This indicates that differences in the coagulation–fibrinolysis system must exist between the leiomyoma tissue and smooth muscle tissue. After UAO, reperfusion occurred in conjunction with thrombolysis in the myometrium, but reperfusion did not occur in leiomyoma tissues. Therefore, the blood supply in a fibroid cannot resume, and results in its death.

The difference in calcium concentration response to uterine ischemia

Intracellular free calcium ($Ca2^+$) is an important second messenger in the intrinsic cell apoptosis pathway. An overload of $Ca2^+$—which is regulated by the inositol trisphosphate receptor (IP3R) and ryanodine receptor (RYR) in sarcoplasmic reticulum membrane—increases the release of cytochrome c (Cytc) into the cytoplasm and initiates a downstream caspase cascade, and ultimately leads to apoptosis. Yang et al[16] report that IP3R1 and RYR1 mRNA and protein levels are significantly higher in fibroid tissue than in myometrial tissue. Under hypoxic conditions, the $Ca2^+$ concentration is significantly higher in fibroid cells than in myometrial cells, which induces apoptosis in uterine fibroid cells and is responsible for the susceptibility of fibroid cells to apoptosis under UAOL.

"Single organ shock" and "ischemic infarction"

Lichtinger et al[13] and Burbank and Hutchins[14] initially proposed the "transient uterine ischemia" hypothesis to explain the therapeutic mechanism of UAO. They proposed that, after artery occlusion, ischemic infarction occurs in myomas of the uterus, which results in leiomyoma cell death and significantly reduces the volume of the uterus and fibroids. They further proposed that UAOL and UAOE may share this physiological process. However, since this proposal, some scholars have begun to believe that UAOL and UAOE may have different mechanisms.[7,17] In 23 patients who underwent UAOE and 17 patients who underwent UAOL, Park et al[18] found that the two kinds of approaches can reduce the volume of the uterus and effectively alleviate postoperative menorrhagia symptoms. Necrotic cells were present only in patients who underwent UAOE, and cell apoptosis was present 6 months after surgery in one patient who underwent UAOL.

When tissue is injured because of ischemia–reperfusion, apoptosis and necrosis are two different forms of cell death that often occur. The intensity and time of the injury of ischemia reperfusion are responsible for the different results of cell death. Cheng et al[17] found apoptotic cells in leiomyoma and smooth muscle tissue specimens from patients who underwent UAOL. However, the number of apoptotic cells was significantly greater in leiomyoma tissue than in smooth muscle tissue, and increased more quickly in leiomyoma tissue, along with the duration of hypoxia. These outcomes suggest that leiomyoma cell death after UAOL primarily depends on the cell apoptosis pathway, which is different from the ischemic infarction pathway after UAOE. Therefore, Cheng et al[17] proposed the hypothesis of "single organ shock–uterine shock" to explain the therapeutic mechanism of UAOL. The pathophysiological process of "uterine shock" after the occlusion of the uterine artery is the following: after occluding the uterine artery, cell apoptosis occurs because of ischemia and hypoxia, and then the uterus gradually recovers its physiological ability with the restoration of the uterine blood supply. In this process, leiomyoma death by the cell apoptosis pathway occurs because of the inability of the tissue to tolerate hypoxia, but the uterus survives because of the special compensatory blood supply and/or the coagulation–fibrinolysis system.

Compared to ischemic infarction of leiomyoma cells after UAOE, the process of UAOL is more "moderate," which may be related to the retention of intact uterine blood vessels and relatively easier reperfusion after UAOL. The incidence of postoperative pain and infection is higher in patients treated by UAOE than by UAOL. A study of 24 patients who underwent UAOE and 22 patients who underwent UAOL shows that the incidence of postoperative pain during the follow up of 6 months was significantly higher and the dose of analgesic drugs use was greater in the UAOE group than in the UAOL group ($p = 0.008$). Park et al[18] compared 23 patients who underwent UAOE with 17 patients who underwent UAOL. Fifteen percent of patients had fever after the UAOE operation. The incidence of postoperative pain was 30%. The bleeding rate was 54% in the UAOE group, whereas the bleeding rate was only 20% in the UAOL group, and the UAOL group patients did not have postoperative fever or obvious pain. In a study by Ambat et al[19] of 20 patients with symptomatic uterine leiomyomas, 10 patients underwent UAOE and the remaining 10 patients underwent UAOL. They were followed up for 6 months. The relief rate of menorrhagia, the uterine size, and the reduction in the volume of the dominant fibroid were not significantly different between the two groups ($p = 0.436$, $p = 0.796$, and $p = 1.0$, respectively), but the incidence of postoperative pain was higher in the UAOE group than in the UAOL group ($p = 0.0002$).

The influence on ovarian function and fertility after UAOL

Studies on the blood supply to the ovaries are relatively few. Limited papers demonstrate that 40% of the blood supply for the ovaries comes from the ovarian artery, 56% from the roots from ovarian and uterine arteries, and only 4% from the uterine artery. The blood supply for the ovaries would theoretically decrease after UAOL and would involve ovarian function. However, blood flow serving the ovaries through the ovarian artery is not destroyed. In addition, there is full of the vascular communication between the uterine artery, round ligament artery, ovarian artery, inferior epigastric artery, and so forth. Therefore, blood can flow into the ovaries through anastomotic vessels from the artery of round ligament. According to some reports, 1 month after UAO by laparoscopic bipolar coagulation, the levels of hormones [e.g., follicle-stimulating hormone (FSH), luteinizing hormone, estradiol] in 96.4% patients are statistically insignificant, compared to the preoperative levels.[5] The level of FSH increased in 3.5% patients (> 30 mIU/mL) with clinical manifestations of menopause. Lee and his team[20] performed UAOL for 44 patients with symptomatic uterine myomas. They examined FSH levels in the blood before surgery and 1 month after surgery. The average level of FSH increased from 5.5 IU/L before surgery to 8.7 IU/L after surgery. However, the result was statistically insignificant because the FSH level of only 5% patients was > 10 IU/L. A study by Cheng et al[9] showed that the incidence of amenorrhea after UAOL-M was 1.3% (4/348 patients; average follow-up time, 28.2 months), and after LM was 2.1% (3/172 patients). The difference was statistically insignificant, and amenorrhea occurred over 5 months after UAOL-M surgery. This finding suggests that the recent reserve function of the ovary is not involved after UAO.

It is difficult to assess the outcomes of fertility and pregnancy for UAO patients because most of these patients have no fertility requirements. By contrast, the time and age of postoperative pregnancy are also uncertain factors. Therefore, estimating the rate of pregnancy after UAO is truly difficult. Walker and McDowell[21] report that, among 108 patients who tried to become pregnant after UAOE, 33 patients had a successful pregnancy (pregnancy rate, 39.5%; mean age, 37 years). Mara[7] report that in a group of patients who wanted children after UAOL (mean age, 34.9 years), the postoperative pregnancy rate was 67%, and 46% of patients had a successful delivery. Liu et al[22] compared 84 patients who underwent UAOL-M with 83 patients who underwent LM, and their results suggested that the postoperative uterine artery blood flow and pregnancy rates were not statistically significant. A survey of the Jefferson Medical College (Philadelphia, PA, USA) showed that the incidence of postpartum hemorrhage, premature delivery, cesarean section, and fetal malpresentation were significantly higher in pregnant patients who underwent UAOE than in the normal population.[26] Holub et al[23] compared the outcomes of pregnancy between 38 patients who underwent UAOL and 20 patients who underwent UAOE. Spontaneous abortion and the pregnancy rate were significantly higher after UAOE (56%) than after UAOL (10.5%). The rate of fetal anomalies and cesarean sections were higher in the UAOE group than in the UAOL group, but the difference was not statistically significant. The preterm birth rate was also higher in the UAOE group (15.3%) than in the UAOL group (20%; $p = 0.0613$).

The intra- and postoperative complications of UAOL

Certain technical difficulties exist for dissecting, separating, and blocking the uterine artery under laparoscopy. Physicians should be careful to avoid injuring the basin wall, iliac vessels, and ureter.[3,9] We often choose the initial part of uterine artery as the site to block the vessel, primarily because of the clear anatomical landmarks and few injuries to the pelvic iliac vessels and ureter. Most postoperative complications include pain, infection, fever, vaginal bleeding, deep vein thrombosis, and amenorrhea. Helal et al[8] found that 22 of 45 patients who underwent UAOL had an increased risk of postoperative vaginal discharge, possibly because of a submucosal myoma; however, the duration of vaginal discharge was generally < 1 week. One patient returned to the hospital 1 week after the operation because of a serious complication (i.e., unilateral deep vein thrombosis in a lower extremity) and received symptomatic treatment; her prognosis was good. Cheng et al[9] studied 348 patients who underwent UAOL in combination with myomectomy for symptomatic fibroids. No severe damage such as ureter or/and pelvic vascular injuries occurred; however, there were other complications such as one case of subcutaneous emphysema, one case of vaginal bleeding, and two cases of intestinal obstruction. All patients recovered smoothly 1 week after symptomatic treatment. Five months after the operation, amenorrhea occurred in four (1.1%) patients. Lee et al[24] report no serious complications during and after the UAOL operation in 44 patients. Kuzel et al[25] report that the UAOL group had only 2.7% cases of intrauterine necrosis, which was verified by hysteroscopic examination.

Summary and prospect

The clinical outcomes of UAOL in the treatment of symptomatic uterine fibroids are satisfactory. Uterine artery occlusion by laparoscopy helps improve operative quality, improves postoperative symptoms, and broadens the indications for LM. The mechanism of the treatment is related to the characteristics of the uterine blood supply, the differences in coagulation–fibrinolytic system, and the hypoxia tolerance between uterine leiomyoma tissue and uterine smooth muscle. The short-term follow-up study shows no significant changes in the ovarian reserve function after UAOL. However, patients who become pregnant after UAO may have a higher risk of postpartum hemorrhage, premature delivery, cesarean section, and fetal abnormalities. To assess the overall effects of UAOL technology, further random study on the clinical results during long-term follow up, as well as its therapeutic mechanism of UAOL, are needed in the future.

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