Yonsei Medical Journal
Vol. 44, No. 4, pp. 694 - 702, 2003

Treatment Outcomes of Uterine Artery Embolization and Laparoscopic Uterine Artery Ligation for Uterine Myoma

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In treating women with leiomyoma and who wish to preserve their uterus, laparoscopic uterine artery ligation or uterine artery embolization should be considered as possible options. This study was performed to evaluate the efficacy of laparoscopic uterine artery ligation and uterine artery embolization in treating uterine myoma. The treatment outcomes of 23 patients who underwent uterine artery embolization and 17 laparoscopic uterine artery ligation were evaluated. The uterine volume reduced 3 months after uterine artery embolization, but thereafter no significant changes were observed. On the other hand, the uterine volumes were only slightly reduced 3 months after laparoscopic uterine artery ligation, and slightly more reduced 6 months later. The average reduction in the case of laparoscopic uterine artery ligation was about 58.5%. After laparoscopic uterine artery ligation, 20% of the patients complained of vaginal spotting. Furthermore, the mechanism of volume reduction was evaluated using specimens obtained from a biopsy taken after each procedure. The results suggested that laparoscopic uterine artery ligation results mainly in physiologic cell death, that is apoptosis, whereas, the corresponding result is cell necrosis for uterine artery embolization. Uterine artery embolization and laparoscopic uterine artery ligation are both effective in relieving the symptoms caused by uterine myoma, and therefore both procedures can be used in place of hysterectomy or myomectomy.

Key Words: Uterine leiomyoma, treatment outcome, laparoscopic bilateral uterine artery ligation, uterine artery embolization

Received April 14, 2003
Accepted May 23, 2003

** The present study was supported by the CMB-YUHAN research grant from Yonsei University College of Medicine for 2000. (No. 2000-03)*

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INTRODUCTION

Leiomyoma is one of the most common pelvic tumors and its incidence is reported to be 20 - 40% in women over 35 years old.[1] Among the available modalities for treating leiomyoma, hysterectomy is the preferred and most frequently performed method. There are many possible approaches to performing hysterectomy, including total abdominal hysterectomy, vaginal hysterectomy, total laparoscopic hysterectomy, and laparoscopically assisted vaginal hysterectomy.

However, for those patients who strongly wish to preserve their uterus, myomectomy is substituted for hysterectomy, and is performed using one of several approaches.

However, there is some controversy surrounding the use of this procedure, with many researchers reporting that myomectomy, especially when removing multiple myomas, results in increased blood loss, prolonged operating time, postoperative complications, and a prolonged hospital stay.[1] Moreover, about 20 - 25% of myomectomy cases have to be changed to hysterectomy intraoperatively due to causes which are explained in detail in prior studies. Furthermore, myomectomy is not a viable option in cases where the myoma is situated close to the endometrium or is occupying most of the uterus.

Thus, as a method of conservative management, hormonal therapy has been established. Progesterone and gonadotropin releasing hormone agonist is highly effective in reducing pain and myoma volume, but their limitation lies in the fact

that the myoma resumes proliferation once the hormones are removed.[1] Moreover, long-term hormonal therapy may lead to osteoporosis, menopausal symptoms and amenorrhea. On account of such limitations, hormonal treatment is only used as a preoperative therapy.

Since the introduction of transarterial embolization by Heaston, et al. in 1979 for managing obstetrical hemorrhage, the procedure has been widely used in the field of gynecology.[2] Ravina, et al. reported a successful outcome in treating symptomatic myoma by performing uterine artery embolization[3,4] and, according to other reports, transarterial embolization not only reduces the patient's symptoms by 60 - 80%, but also reduces myoma size by 40 - 50%.[5-7]

As an alternative method of obstructing the uterine blood flow, uterine artery ligation should also be considered. Lin et al. reported the effective management of myoma with laparoscopic bilateral uterine arteries ligation in 2000.[8]

Nevertheless, the exact mechanisms of uterine artery embolization and ligation involved in reducing myoma size have not been clearly identified. Therefore, the present study was performed to evaluate the treatment efficacies of uterine artery embolization and laparoscopic uterine artery ligation in myoma patients and to clarify the mechanisms involved in size reduction in terms of cell apoptosis and necrosis.

MATERIALS AND METHODS

Patients

Forty patients diagnosed with uterine myoma by ultrasonography from January 1999 to October 2000 at the Department of Obstetrics and Gynecology, Yonsei Medical Center, Seoul, Korea, were included in this study. Twenty-three of the patients were treated by uterine artery embolization and 17 by laparoscopic uterine artery ligation. Myoma specimens were obtained from 1 and 3 patients at 6 months following ligation and embolization, respectively. As a control group, myoma specimens were obtained from 13 patients during transabdominal hysterectomy. All surgical specimens were stored at -70℃.

Preoperative evaluation

The baseline uterine and myoma sizes were measured by ultrasonography and their volumes were calculated as follows[9]; maximum length × maximum transverse diameter × maximum antero-posterior diameter × 0.523. Bleeding scores were calculated from the menstrual flow diary recorded by the patients.[10]

Operative procedures

Uterine artery embolization

Following pelvic arteriography, performed using a 5-F Levin-1 catheter (Cook, Bloomington, MA, USA) or 4-F C1 Glidecath (Megatech/Boston Scientific, Watertown, MA, USA), to identify the uterine arteries, bilateral selective uterine artery catheterization was performed with the catheter tips placed within the anterior branch of the internal iliac artery. Polyvinyl alcohol particles (PVA particle, 500-700 μm, Cook, MA, USA) or gelfoam were used to embolize the uterine vascular bed.

Laparoscopic uterine artery ligation

Under general anesthesia, a 1 cm sized curvilinear incision was made below the umbilicus. The abdomen was insufflated with 2.0 L of carbon dioxide through a subumbilically inserted Veress needle. Two additional 5 mm cannulas were inserted under direct vision over the left and right lower quadrants. The bilateral ureters were identified and then the pelvic peritoneum overlying the uterine artery was dissected. The uterine artery was grasped with atraumatic forceps and was ligated with a clip. In some patients, the parauterine collateral vessels were coagulated.

Follow-up

All patients were told to record any perceived symptoms. At 3, 6, and 12 months following the procedure, ultrasonography was done to measure the uterine and myoma volumes, information regarding the clinical symptoms was obtained and the patient's bleeding score charts were collected.

Analysis of cell necrosis and apoptosis

Immunocytochemical staining of the specimens obtained from the patients was performed to observe cell necrosis. TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP-gigoxigenin nick end-labeling) was performed to identify apoptosis. Tissue sections were placed in ethanol for 10 min. Protein digestion was done with proteinase K, and the specimens were then rinsed, followed by quenching with peroxidase contining 1% H_2O_2 in PBS. TUNEL was performed using an apoptosis detection kit (ApopTag: Oncor, Gaithersburg, MD, USA). The samples were incubated with anti-digoxigenin conjugated to peroxidase and visualized using DAB and H_2O_2. Counterstaining with hematoxyline and dehydration were performed, followed by mounting. Apoptic cells were counted under a microscope at × 400 magnification, and the results were expressed as a percentile before being interpreted as being either positive or negative. The samples were evaluated for LCA (leukocyte common antigen) using a similar procedure.

Statistics

The volumes of the uteri and the myomas were obtained before and 3, 6 and 12 months after each procedure. The mean values and standard deviations were also calculated. The paired t-test was used to evaluate the statistical differences and a p value of less than 0.05 was considered to be statistically significant.

RESULTS

Patients' characteristics

Out of the total of 40 patients, 23 underwent uterine artery embolization and 17 laparoscopic uterine artery ligation. In 13 out of 17 patients from the ligation group, the ovarian arteries and collateral vessels were cauterized simultaneously with uterine artery ligation. The mean ages of the embolization and ligation groups were 41.2 ± 2.0 and 39.2 ± 3.3 years, respectively. Menorrhagia (37%), infertility (30%) and tenderness (69%) were the main symptoms of the ligation group, whereas menorrhagia (98%) and tenderness (30%) were the main symptoms of the embolization group. 95% and 92% of the patients experienced an improvement in their symptoms at 6 months following laparoscopic uterine artery ligation and uterine artery embolization, respectively.

Complications related to embolization were fever (15%), pain (30%) and bleeding (53.8%), whereas bleeding (20%) occurred in the ligation group (Table 1).

Change in myoma size following uterine artery embolization

The average sonographic myoma volume before the procedure was 212.01 ± 21.1 cm^3, whereas this fugure significantly decreased to 149.3 ± 2.0 cm^3 3 months after the procedure was performed (p=0.01). A further reduction in size was noted 6 months after the procedure, although this difference was not statistically significant (Table 2).

Table 1. Patients' Characteristics

	Uterine artery embolization (N=23)	Laparoscopic uterine artery ligation (N=17)
Age	41.2 ± 2.0	39.2 ± 3.3
Symptoms	menorrhagia (37%) infertility (30%) pain (69%)	menorrhagia (98%) pain (30%)
Symptom relief	95.6%	92%
Side effects	fever (15%) pain (30%) bleeding (53.8%)	bleeding (20%)

Table 2. Uterine Volume Change after Uterine Artery Embolization

Time (months)	Uterine volume (cm^3)	*p*-value*
Preop	212.01 ± 21.1	-
Postop 3	149.30 ± 2.0	0.01
Postop 6	154.10 ± 35.0	0.07

Preop, preoperative; Postop, postoperative.
*$p<0.05$ by independent 2-sided t-test from the value of preop.

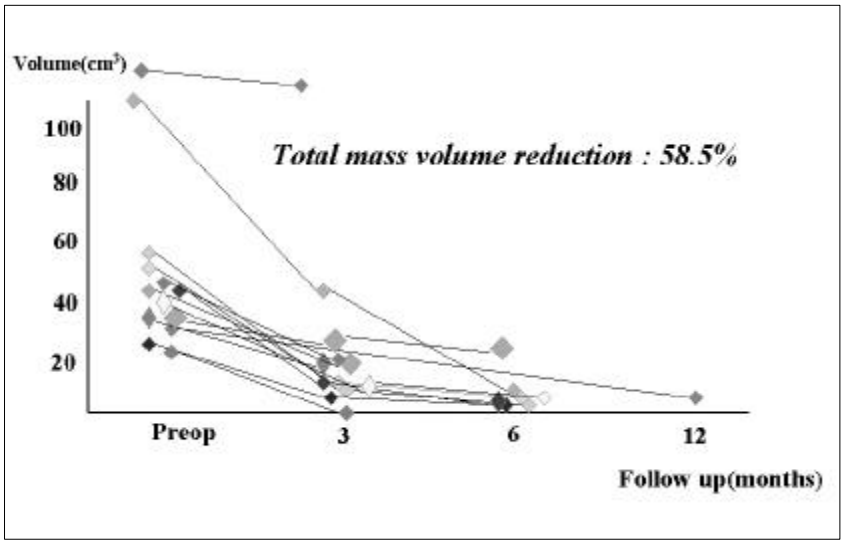

Fig. 1. Myoma volume change after uterine artery embolization.

The total mass reduction was 58.5% in 10 patients with clearly delineating margins being observed on ultrasonography, which enabled a total follow up period of 12 months (Fig. 1).

Change in myoma size following laparoscopic uterine arteries ligation

Among the 17 patients who underwent bilateral uterine arteries ligation, 13 also had collateral vessels originating from the ovarian arterioles. In the case of these 13 patients a significant volume reduction occurred from 224.48 ± 191.94 to 188.44 ± 74.00 cm^3 at 3 months and 146.83 ± 74.00 cm^3 at 6 months after the procedure (p=0.038, 0.05). Myoma size reduction was also observed in those patients who only underwent uterine arteries ligation, but the difference was not statistically significant (Table 3). The total mass reduction was 56.0% in the 17 patients, with clearly delineating margins on ultrasonography, which enabled a total follow up period of 12 months (Fig. 2).

Changes in bleeding chart scores

As shown in Table 4, the scores were reduced by 87.6%, 70.5%, and 60.9% at 6 months following embolization, ligation with collateral block, and ligation without collateral block, respectively.

Apoptosis expression in myoma tissue

TUNEL staining of the myoma tissues obtained from the untreated patients, those who underwent uterine arteries embolization, and those who underwent ligation showed positive, negative, and trace results in the expression of apoptosis, respectively (Fig. 3). LCA positive inflammatory cells were noted in the myoma specimens obtained at 6 months after both embolization and ligation.

Table 3. Volume Change after Uterine Artery Ligation with or without the Collateral Vessels being Cauterized

Time (months)	Uterine volume (cm^3)			
	Cauterized (n=13)	*p*-value	Not cauterized (n=4)	*p*-value*
Preop	224.48 ± 191.00	-	160.92 ± 27.28	-
Postop 3	188.44 ± 98.23	0.038	131.49 ± 10.74	0.139
Postop 6	146.83 ± 74.00	0.050	104.51 ± 23.42	0.435
Postop 12	157.56 ± 56.38	0.216	-	-

Preop, preoperative; Postop, postoperative.
*$p<0.05$ by independent 2-sided t-test from the value of preop.

Table 4. Changes of Bleeding Chart Scores

	Preop. score	Postop. score	Reduction rate
LUAL+Collaterals cauterization	146.75	43.50	70.5%
LUAL alone	267.25	104.25	60.9%
UAE	380.29	47.29	87.6%

LUAL, Laparoscopic uterine artery ligation; UAE, Uterine artery embolization.

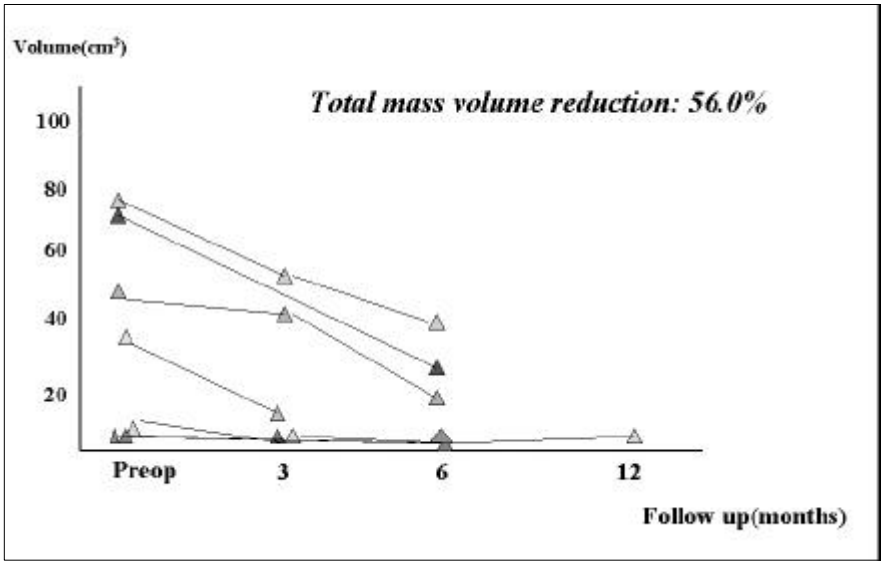

Fig. 2. Myoma volume change after laparoscopic uterine artery ligation.

DISCUSSION

Uterine artery embolization and laparoscopic uterine artery ligation are not widely applied treatment modalities in leiomyoma. No information regarding their mechanisms and long-term outcomes is available as yet, and moreover, the efficacy of laparoscopic uterine artery ligation is still unproven.

Radiologic transarterial embolization was introduced in the late 1960s to treat pelvic hemorrhage following trauma or radiotherapy,[11,12] and took the form of uterine artery embolization in 1979 for the hemostasis of postpartum hemorrhage.[2] There-

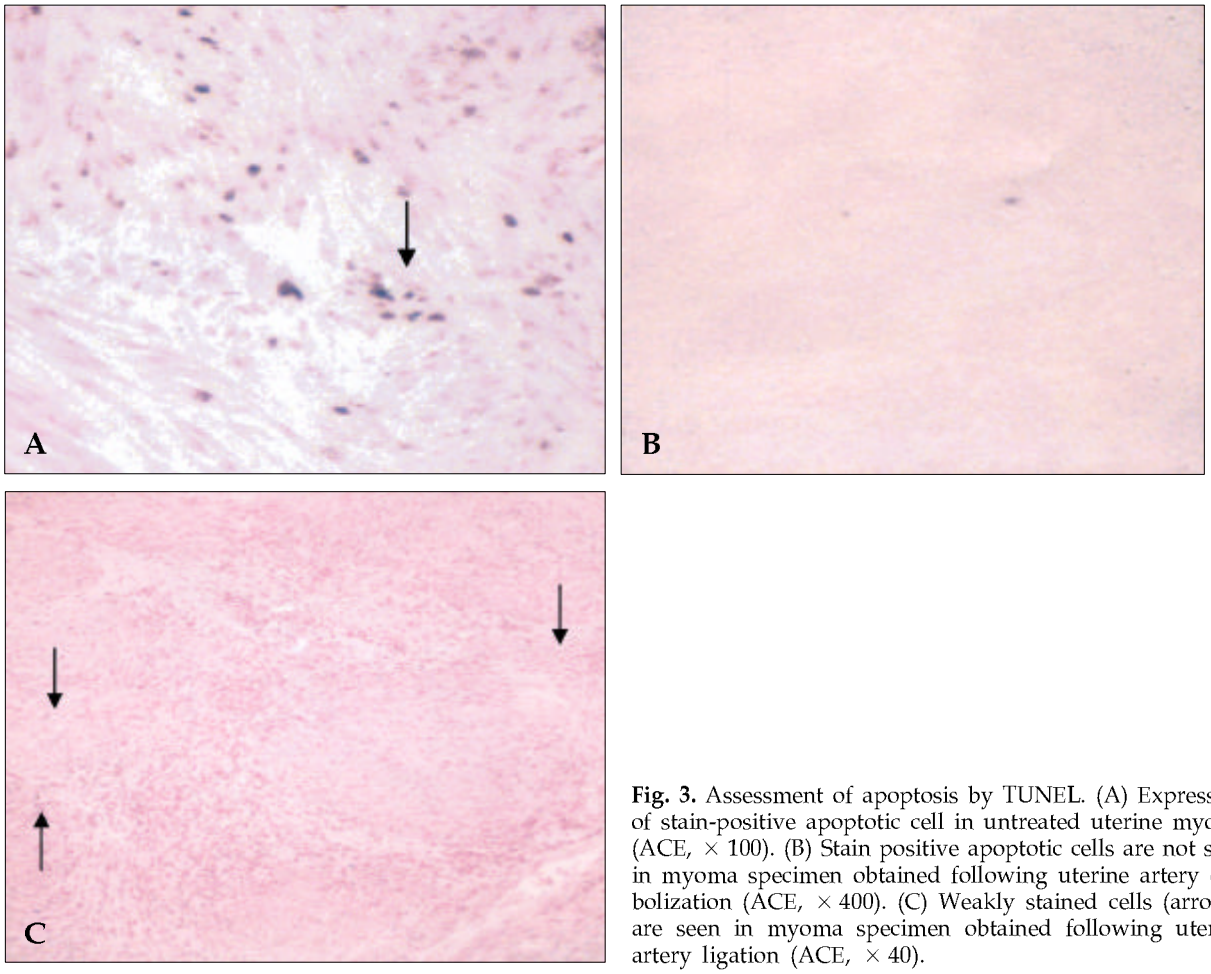

Fig. 3. Assessment of apoptosis by TUNEL. (A) Expression of stain-positive apoptotic cell in untreated uterine myoma (ACE, × 100). (B) Stain positive apoptotic cells are not seen in myoma specimen obtained following uterine artery embolization (ACE, × 400). (C) Weakly stained cells (arrows) are seen in myoma specimen obtained following uterine artery ligation (ACE, × 40).

after, uterine artery embolization began to be used for postpartum and posthysterectomy bleedings. Ravina et al were the first to report the use of uterine artery embolization in myoma treatment, initially using it for preoperative and postoperative symptoms control, and subsequently using the procedure to perform surgery-free myomectomy.[13] Many studies followed in favor of uterine artery embolization in the treatment of myoma and, to date, it is considered one of the most effective and safest therapeutic modalities for patients with symptomatic myoma. The procedure time is about 45 to 60 minutes and the total radiation dose incidentally administered to the ovaries is about 120 rad which is below the threshold dose known to induce ovarian failure.[14] However, it can only be performed by radiology specialists and the learning curve required to achieve a success rate of at least 90% is very steep.[15,16] About 6 - 7% of the patients complain of fever, inflammation, and pain following the procedure, which last for up to 2 months.

Considering the fact that laparoscopic techniques are often in the field of gynecologic surgery, laparoscopic uterine artery ligation is likely to attract considerable interest in the near future. In order to perform a successful laparoscopic uterine artery ligation, the surgeon has to be equipped with the necessary laparoscopic skills and should be able to precisely locate the uterine artery in order to correctly ligate the vessels. If these prerequisites are not met, massive bleeding may ensue, thus necessitating laparotomy.

Cell death consists of cell necrosis and apoptosis. Therefore, the death of leiomyoma cells following the obstruction of uterine blood flow could be caused by either necrosis or apoptosis. Cell injury usually takes place during the process

of hypoxia and reperfusion.[17] The degree of cell death depends not on the duration of hypoxia, but occurs during the reperfusion following acute hypoxic injury. Apoptosis mainly occurs under hypoxia, but abrupt ischemia induces cell necrosis.

In 1997, Yutaka, et al.[18] observed necrotic cell death under chemical hypoxia conditions, which were induced by hindering mitochondrial respiration and glycolysis, and when the cells were restimulated with Fas/Apo-1, the presence of tumor necrosis factor, DNA damaging reagents, Ca^{+2} ionophores, and apoptosis were noted. In other words, either necrosis or apoptosis can be induced from the same cells using different triggering factors and mechanisms. Cell necrosis and apoptosis are differentiated by the difference in the intracellular ATP levels, which rapidly decreases in the former and rapidly increases in the latter. Apoptosis and necrosis can occur simultaneously within the tumor. For instance, cells deprived of adequate oxygen undergo glycolysis leading to a decline of intracellular ATP levels, and eventually cell necrosis occurs instead of apoptosis.

Hence, it could be said that the intracellular ATP level plays an important role in determining the mechanism of cell death.

Intracellular ATP may be considered as a form of energy produced by oxygen, thus hypoxic cells, once reoxygenated, proceed to apoptosis instead of necrosis owing to the elevation of the intracellular ATP levels. The relationship between cell apoptosis and reoxygenation has previously been hypothesized as a form of ischemic injury through Fas-ligand expression that eventually activates pro-IL-1β, and oxygen-free radicals.

As expected, cell necrosis was observed up to 6 months after uterine artery embolization, implying that the procedure induces acute ischemia that persists for at least 6 months. It could also be assumed that re-oxygenation had not occurred during that time, since no apoptosis was observed in the postoperative specimen. However, the question remains as to when the collateral flow via the ovarian artery develops, and when it does, will it significantly contribute to myoma regrowth and apoptosis

As shown in the present study, a significant volume reduction of 29.6% in the uterus and 58.5% in the myoma at 3 months following uterine artery embolization were achieved, which lasted beyond 6 months with no recurrence. Current observations imply that myoma re-growth due to reperfusion, or energy supplementation, had not occurred after artery embolization.

Among the uterine artery ligation group, those patients who had their collateral vessels originating from the ovarian artery cauterized showed better clinical results. The overall myoma volume reduction in the ligation group was 50.6%. An interesting finding was made in this group in that, unlike in the embolization group, a trace of cell apoptosis had been observed at 6 months, implying that re-oxygenation had occurred following the procedure. Thus, the possible existence of differences in the mechanism of myoma regression between the two procedures has to be assumed.

According to April, et al.,[17] following uterine artery ligation, initial ischemic reaction takes place and cells under ischemic environment produce several chemokine and adhesion molecules inducing inflammation. In our study, LCA positivity- a sign of inflammation due to ischemia- was observed in the tissues obtained following both uterine artery ligation and embolization. Therefore, it could be said that both of the procedures led to the obstruction of blood flow, resulting in cell death due to persistent ischemia and, eventually, the reduction of the myoma and uterus volumes. The association of collateral perfusion via the ovarian artery or collateral vessels with re-oxygenation is still not clear, but rather the collateral perfusion is though to be related to treatment failure. Based on our experience with 13 patients who had their collateral vessels cauterized concurrently with uterine artery ligation, reperfusion via the ovarian artery does not seem to contribute to cell apoptosis. Thus, angiogenesis of the collateral vessels in women with myoma re-growth after ligation does not appear to be the initiating event, but rather the consequence.

Severe pain following uterine artery embolization was encountered in 30% of the patients, whereas no one in the ligation group complained of such cramps.

Severe pain is known to be related to abruptness and aggressiveness of ischemic status. During uterine artery embolization, ischemia is

initiated at the time of catheter insertion into the femoral artery. And once the catheter tip has been placed in the uterine artery, the diameter of the tip is wide enough to obstruct the flow. Moreover, polyvinyl alcohol or gelfoam administration induces abrupt and severe ischemia.[19] Thus, severe pain that follows uterine artery embolization could be explained by the aforementioned process. In contrast, the ischemic process is relatively slow and gradual during uterine artery ligation, because prior to ligating the artery, time consuming steps, such as the dissection of the periarterial tissue and the manipulation of the artery, allow the myoma cells to gradually prepare for the ischemia.

To sum up, the distinctive difference in the ischemic process between uterine artery embolization and ligation is that, unlike the abrupt and severe cell ischemia which occurs following the former procedure, slow and gradual cell ischemia takes place following the latter procedure. In uterine artery ligation, the myoma cells, having acquired sufficient energy through microvasculature and unknown chemical mechanisms during the time-consuming steps required to ligate the bilateral uterine arteries, thus recover their ATP pool ensuing cell apoptosis along with cell necrosis. Data comparing the clinical outcomes of uterine artery ligation and embolization is still lacking and, in light of this, the current study was performed to compare the outcomes of these two procedures, and efforts were made to observe the differences in the mechanism of cell death in each procedure. Based on our current observations, uterine artery embolization and laparoscopic uterine artery ligation are both effective in relieving the symptoms and reducing myoma volume, and could replace hysterectomy for those who wish to preserve fertility. Both procedures are associated with cell necrosis and apoptosis, and laparoscopic uterine artery ligation, in particular, induces fairly gradual and persistent volume reduction through physiologic cell death, apoptosis.

Further investigation is needed to elucidate the differences in the mechanism of volume reduction and to compare the clinical outcomes between laparoscopic uterine artery ligation and transarterial uterine artery ligation with a longer follow-up period and a larger study population.

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