·Clinical Research·

Influences of lymphatic vessel ligation in pelvic lymphadenectomy on postoperative lymphocyst formation: a randomized controlled trial

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[**Abstract**] **Background and Objective:** Pelvic lymphocysts are the most common postoperative complications of pelvic lymphadenectomy. Prevention of this disease is more important than treatment. This randomized study was to evaluate the preventive effect of lymph vessel ligation during pelvic lymphadenectomy on pelvic lymphocyst formation. **Methods:** A total of 39 patients with gynecologic malignancy, who had pelvic lymphadenectomy in the Second Affiliated Hospital of Sun Yat-sen University from July 2006 to January 2007, were randomized into the ligation group (19 patients) and the non-ligation group (20 patients). All patients had no heart disease, hepatopathy, nephronia, pneumonopathy, hypoproteinemia and no history of radiotherapy. All the patients were followed-up with sonographic evaluation and physical examination for lymphocysts and other postoperative complications at 1, 4, 12, and 24 weeks after operation. **Results:** No significant differences were observed between the two groups in pathlogic type, age, height, weight, body surface area, body mass index (BMI), operation duration, estimated blood loss, time to the passage of flatus, total drainage volume, duration of drainage, and duration of hospital stay (P>0.05). The occurrence rate of lymphocysts was significantly lower in the ligation group than in the non-ligation group at one week after operation (26.3% vs. 60.0%, P<0.05). The rates were slightly lower in the ligation group than in the non-ligation group without significant differences after then (31.6% vs. 55.0% at the 4th week), (16.7% vs. 45.0% at the 12th week), (20.0% vs. 27.8% at the 24th week). No significant differences were observed in the occurrence of other postoperative complications between the two groups (P<0.05). **Conclusions:** Ligations of the deep inguinal lymph vessels, obturator lymph vessels, common iliac lymph vessels, and the lymph vessels at the crossing of the external iliac and the inter iliac vein can decrease the occurrence of postoperative lymphocysts in short-term period, and will not increase the occurrence of postoperative complications.

Key words: gynecologic neoplasm, surgical procedures, pelvic lymphadenectomy, lymphocyst, postoperative complication

Cervical cancer, ovarian cancer and endometrial cancer are common malignant tumors in female reproductive system, and are mainly treated by operation, chemotherapy, radiotherapy and biotherapy. Although surgical scope and approach vary across different types of tumors, pelvic lymphadenectomy has become an important part of the treatment and surgical staging for gynecologic malignant tumors. Pelvic lymphocyst is a major post-operative complication after pelvic lymphadenectomy, with the incidence range from 5% to 54%.[1,2] Lymphocyst may cause different symptoms depending on its site and size. Currently, the main treatment options for lymphocyst include puncture aspiration, sclerosing agent injection, oral administration and clysis of traditional Chinese medicine, and surgical treatment. All these treatments are painful to some extent. Therefore, prevention of pelvic lymphocyst is even more important. Some established methods are currently used to prevent lymphocyst, including placement of drainage tube,[3] pelvic peritoneal non-closure,[4] use of fibrin sealant,[5] omentoplasty and omentopexy.[6]

Some scientists have also suggested that ligation of the main lymphatic vessels that collected drainage from the lower extremities, namely, ligation of residual external iliac lymphatic tissue and obturator foremen lymphatic tissue, could decrease the occurrence of post-operative lymphocysts.[7] The rationale behind this is that ligation of lymphatic vessels decreases lymphocyst occurrence by blocking lymphatic drainage from the lower extremities and preventing lymph accumulation in the pelvic cavity. However, whether lymphatic vessel ligation actually decreases the occurrence of lymphocysts and whether ligation

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This paper was translated into English from its original publication in Chinese by Guangzhou Liheng Medical Translation and Wei Liu on 2009-10-19.

The original Chinese version of this paper is published in *Chinese Journal of Cancer* 28(11); http://www.cjcsysu.cn/cn/article.asp?id=16156.

Submitted: 2009-04-30; Revised: 2009-06-16

causes lymph accumulation and subsequently lymphoedema in the lower extremities and increases the occurrence of other complications are still unclear. In the hope of seeking for better surgical procedures to prevent pelvic lymphocysts effectively, our study attempted to analyze and compare pelvic lymphocyst occurrence and complication profiles after ligation or non-ligation of pelvic lymphatic vessels during pelvic lymphadenectomy.

Data and Methods

Study subjects

Patients with gynecologic malignant tumors who received pelvic lymphadenectomy from July 2006 to June 2007 in the gynecology and obstetrics unit of the Second Affiliated Hospital of Sun Yat-sen University were selected. Inclusion criteria were as follows: 1) major heart, lung, liver and kidney diseases were excluded in pre-operative examinations; 2) hypoproteinemia was also excluded pre-operatively; 3) radiotherapy-naive before surgery; 4) the patients were operated by the same surgeon.

Randomization

A randomization chart was produced by the statistical software SAS 8.0. By matching the randomization chart and the chronological order of the surgery for the patients, they were assigned to ligation group or non-ligation group.

Surgical approaches

Pre-operative preparation At one day before operation, 200 mL of 20% mannitol and 1 000 mL of 5% glucose saline were given orally. At the night before surgery, enema with 0.2% soap suds was given for bowel cleaning.

Anesthesia All patients were given tracheal intubation and general anesthesia. Fentanyl and isopropylphenol were used for rapid induction of anesthesia and isoflurane used for maintenance during operation.

Surgical procedures When anesthesia was established, primary tumor resection and pelvic lymphadenectomy were performed as routine. For endometrial cancer and ovarian cancer, (extensive) hysterectomy was first performed, followed by pelvic lymphadenectomy. As for cervical cancer, pelvic lymphadenectomy was given before hysterectomy. During lymphadenectomy, lymphatic tissue was removed entirely. According to randomization assignment, bilateral deep inguinal lymph vessels, proximal and distal obturator lymph vessels, common iliac lymph vessels, and the lymph vessels at the crossing of the external and internal iliac veins were ligated using silk thread (#7) in ligation group; no ligation of the lymph vessels was given in non-ligation group. Posterior pelvic peritoneum was not closured and no fibrin sealant was used. At the end of operation, a double-lumen abdominal tube was placed via the abdominal incision into the previous recto-uterine pouch.

Diagnostic criteria and post-operative examinations for pelvic lymphocyst

At 1, 4, 12, and 24 weeks after operation, patients were given physical examination and B ultrasonic examination to evaluate whether pelvic lymphocyst or other relevant complications occurred.

Diagnostic criteria for pelvic lymphocyst were as follows: echoless area or fluid sonolucent area in the pelvic cavity or inguinal area was detected by B ultrasonic examination, with well-defined boundary, homogenously distributed spots in the area and regular or irregular shape (Fig. 1); echo might be strengthened in the boundary in some cases; the possibility of pelvic blood vessels was excluded by coronary and sagittal scanning. Maximal diameters of the lymphocysts were measured three times and mean values were calculated.

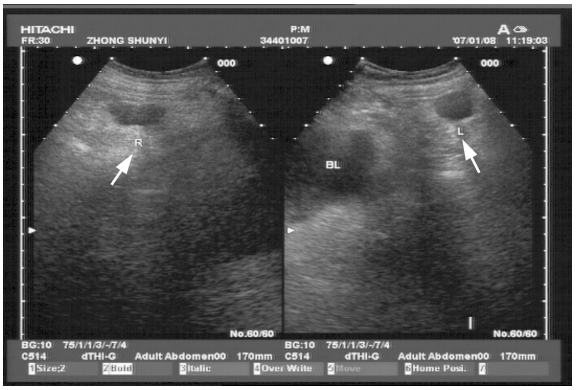

Figure 1 The ultrasonography of the lymphocysts after operation

One week after operation, lymphocysts formed in the patient. An anechoic area (arrow), in oval shape, with clear boundary and well distributed internal light-spot, can be seen in each iliac fossa. Both anechoic areas are not pelvic vessels and the diagnosis of lymphosysts is confirmed by ultrasonography through coronal section and sagittal section.

Statistical methods

Statistical software package SPSS13.0 was used for the statistical analysis. All measurement data were shown as mean ± standard deviation. Differences between groups were tested with *t* test. The differences in lymphocyst occurrence between groups were tested with χ^2 test or Fisher's precision test. A value of $P<0.05$ indicated significant difference.

Results

Pathologic type distribution

Of the 19 patients in ligation group, 16 had cervical cancer (14 squamous cell carcinomas and 2 adenosquamous carcinomas), one had ovarian papillary cystadenocarcinoma, one endometrial adenocarcinoma and one vaginal squamous cell carcinoma. Of the 20 patients in non-ligation group, 13 had cervical squamous cell carcinoma; five had ovarian carcinoma (two serous cystadenocarcinoma, two mucious cystadenocarcinoma and one intraperitoneal tumor), one endometrial adenocarcinoma and one vaginal squamous cell carcinoma. No significant difference was seen in pathologic type distribution between two groups ($P>0.05$).

Clinical data

The differences in mean age, height, body mass, body

surface area and body mass index (BMI) between two groups were insignificant (P>0.05) (Table 1).

Table 1 Clinical data of the two groups

Item	Ligation group	Non-ligation group	P
Age (years)	46.5±11.1	44.7±13.1	>0.05
Height (cm)	157.6± 3.4	158.2± 4.2	>0.05
Body weight (kg)	56.4± 9.4	55.6± 7.1	>0.05
Surface area (m^2)	1.6± 0.1	1.6± 0.1	>0.05
Body mass index (kg/m^2)	22.7± 3.7	22.4± 2.7	>0.05
Operation duration (min)	205.0	210.0	>0.05
Estimated blood loss (mL)	250.0	300.0	>0.05
Time to passage of flatus (days)	3.0	2.5	>0.05
Duration of drainage (days)[a]	5.0	5.5	>0.05
Duration of hospitalization (days)	17.0	16.5	>0.05
Total drainage volume (mL)	470.0	302.5	>0.05

[a]The drains were removed when fluid loss was less than 50 mL and the situation lasted for more than 24 h.

In ligation group, radical hysterectomy plus pelvic lymphadenectomy was performed in 16 cases, radical trachelectomy plus pelvic lymphadenectomy in two cases, and staging laparotomy for ovarian cancer in one case. Operation duration was 155–340 min, with a median of 205 min. Blood loss during the operation was 150–1200 mL, with a median of 250 mL. In non-ligation group, radical hysterectomy plus pelvic lymphadenectomy was performed in 14 cases, radical trachelectomy plus pelvic lymphadenectomy in one case, and staging laparotomy for ovarian cancer in five cases. Operation duration was 160–275 min, with a median of 210 min. Blood loss during operation was 100–800 mL, with a median of 300 mL. The differences were insignificant (P>0.05).

In ligation group, time to anus ventilate after operation was 1–4 days, with a median of 3 days; time to extubation was 3–10 days, with a median of 5 days; duration of the first hospitalization was 10–51 days, with a median of 17 days. In non-ligation group, time to anus ventilate after operation was 1–4 days, with a median of 2.5 days; time to extubation was 3–13 days, with a median of 5.5 days; duration of the first hospitalization was 8–59 days, with a median of 16.5 days. The differences were insignificant (P>0.05).

Median drainage volume after operation was 470.0 mL (range, 135–1 500 mL) in ligation group and 302.5 mL (range, 50–2 920 mL) in non-ligation group, with insignificant difference (P>0.05).

Comparison on lymphocyst occurrence in ligation and non-ligation groups

At one week after operation, the occurrence rate of lymphocyst was 26.3% (5/19) in ligation group. At four weeks after operation, one new case was identified, resulting in a rate of 31.6% (6/19). At 12 weeks, the lymphocyst was relieved in three cases; one case was lost to follow-up; the rate was 16.7% (3/18). At 24 weeks, three cases were lost to follow-up, and the rate was thus 20.0% (3/15).

At one week after operation, the occurrence rate of lymphocyst in non-ligation group was 60.0% (12/20). At four weeks after operation, lymphocyst was relieved in one case, and the rate was 55.0% (11/20). At 12 weeks, lymphocyst was relieved in another three cases, with a rate of 45.0% (9/20). At 24 weeks, two cases were lost to follow-up, with a rate of 27.8 (5/18).

At one week after operation, the occurrence rate of lymphocyst in ligation group was significantly lower than that in non-ligation group (P<0.05). Whereas at four, 12 and 24 weeks after operation, the occurrence rate of lymphocyst in ligation group was lower than that in non-ligation group, but the difference was insignificant (P>0.05) (Table 2).

Table 2 Formation rate of postoperative lymphocysts in the two groups

Time after operation	Ligation group	Non-ligation group	P
1st week	26.3%(5/19)	60.0%(12/20)	0.04
4th week	31.6%(6/19)	55.0%(11/20)	0.12
12th week	16.7%(3/18)	45.0% (9/20)	0.06
24th week	20.0%(3/15)	27.8% (5/18)	0.46

During follow-up, one patient was lost in the 12th week and three were lost in the 24th week after operation in ligation group; two were lost in the 24th week after operation in non-ligation group.

Post-operative complications in two groups

In ligation group, one patient with history of type Ⅱ diabetes had poor wound recovery; 11 patients had perineal and lower extremity edema, and ten of them had received pelvic radiotherapy after operation; two patients experienced fever and another one had intestinal obstruction. No urinary obstruction or deep vein thrombosis was recorded.

In non-ligation group, two patients with history of type Ⅱ diabetes and hypertension had poor wound recovery; 11 patients had perineal and lower extremity edema, and ten of them received post-operative pelvic radiotherapy; three patients experienced fever and one had intestinal obstruction. No urinary obstruction or deep vein thrombosis was recorded.

The occurrence rates of these complications were not significantly different between two groups (P>0.05).

Discussion

Lymphatic vessels are important part of the lymphatic system. Female genital organs, including the uterus, oviduct and ovary, are abundant in lymphatic capillaries and lymphatic vessels.[8] Due to the post-peritoneal close space incurred in pelvic lymphadenectomy, previously normal lymphatic circulation is interrupted and lymph backflow disturbed. Lymph collected from the lower extremities outflows via the incision of the

lymphatic vessels and accumulates in the post-peritoneal pelvic cavity, resulting in the occurrence of lymphocysts.

Besides exudation from the surgical wound, the post-operative abdominal drainage in pelvic lymphadenectomy is mostly from dissected but non-closured lymphatic vessels. In this study, the deep inguinal lymph vessels, proximal and distal obturator lymph vessels, common iliac lymph vessels, and the lymph vessels at the crossing of the external and internal iliac veins on both sides were ligated in ligation group. Theoretically, lymph drainage from the lower extremities and perineum was blocked and lymph outflow should not be expected, therefore, lymphocyst should not occur post-operatively. Still, in the post-operative observation, we saw 135–1500 mL of drainage in these patients and lymphocyst occurred in some of them. The reason might be that some small lymphatic vessels or lymphatic capillaries were not ligated.

As reported in literatures, the efficacy of different prophylaxes against post-operative pelvic lymphocyst varies. Currently, a widely recognized approach is non-closure of the pelvic peritoneum. Suzuki et al.[4] also reported a study using partial non-closure of the posterior peritoneum when performing pelvic lymphadenectomy in patients with ovarian cancer and endometrial cancer, and found that the occurrence of post-operative lymphocyst was significantly reduced. Xiong et al.[7] found that the occurrence rate of post-operative pelvic lymphocyst was 8.66% in non-closured posterior peritoneum group and 24.56% in control group, with significant difference. Consensus has never been reached regarding the usage of fibrin sealant during operation. Riss et al.[5] revealed that using fibrin sealant during operation significantly reduced the occurrence of post-operative lymphocyst while remarkably decreased post-operative drainage volume, and therefore suggested routine use of it during operation. However, Scholz et al.[9] and Furrer et al.[10] obtained contrary results. In 2007, Franchi et al.[11] redefined the role of post-operative drainage. They conducted a randomized controlled study in 234 patients with gynecologic cancers and found that the occurrence of post-operative lymphocyst was not significantly different between drainage group and non-drainage group; for patients with a blood loss of less than 3000 mL during operation and no exudation at the end of operation, it was safe and feasible to skip placement of drainage tube. Our study adopted a randomized and controlled design to reduce the influence of non-treatment factors, such as age, operation duration, blood loss and post-operative drainage volume. After operation, patients were followed up for at least 6 months to observe the short-term and long-term impacts of lymphatic vessel ligation on lymphocyst occurrence. Given consideration to the cost-effect for the patients, we used B ultrasonic examination as the diagnostic method, supplemented by clinical physical examination, so as to avoid increasing the financial burden for the patients.

Our results showed that the occurrence rate of lymphocyst at one week after operation was significantly higher in non-ligation group than in ligation group, while at four, 12 and 24 weeks after operation, non-ligation group had higher occurrence rate of lymphocyst than ligation group, but the differences were insignificant. Sheng-Zhang et al.[12] retrospectively analyzed 1,596 patients who received radical operation for gastric cancer, and found that using silk thread to ligete lymphatic vessels ligation (in 829 patients) was more effective than using electrotome to electrocoagulate lymphatic vessels (in 767 patients) in preventing lymph outflow after operation. This finding was generally consistent with the results from our study. In our study, the overall occurrence rate of lymphocyst was 10.4%–43.8%, which was basically consistent with those reported in literatures.[1,2] The lymphocysts mainly occurred within one week after operation and most of them gradually vanished over time, with only a few persistent lymphocysts. The differences in lymphocyst size between groups at all time points of the follow-up were insignificant. For those larger lymphocysts that caused noticeable symptoms for the patients (four patients in ligation group and five in non-ligation group), such as distention and discomfort in the lower abdomen, we used fine needle aspiration to relieve the symptoms. For those asymptomatic lymphocysts, no intervention was given. Franchi et al.[11] reported that the occurrence rate of symptomatic lymphocyst at one year after operation was 0.9% –5.9% . In our study, the occurrence rate of lymphocyst at 24 weeks after operation was 20.0% –27.8% . It was believed that the rate would continue decreasing with time.

It has been reported that pre-operative radiotherapy might give rise to lymphocyst occurrence. Therefore, we defined pre-operative radiotherapy as one of the exclusion criteria, but some high risk patients with cervical cancer and endometrial cancer received pelvic radiotherapy after operation. It was thus necessary to figure out its influence on lymphocyst occurrence. Theoretically, radiotherapy might close certain pelvic lymphatic vessels and thereby impact the establishment and regeneration of the collateral circulation of the lymphatic system. However, most of the lymphocysts in our study occurred within one week after operation, whereas external pelvic radiotherapy generally started at two weeks after operation. Hence, we believed that short-term lymphocyst occurrence in our study was not significantly related to radiotherapy. At 24 weeks after operation, six of eight patients with persistent lymphocysts had post-operative pelvic radiotherapy, while three of ten patients with vanished lymphocysts had received post-operative pelvic radiotherapy (P>0.05). Therefore, it was considered that radiotherapy had no significant impact on the remission of lymphocyst.

Main post-operative complications after pelvic lymphadenectomy were fever, wound infection, poor wound recovery, intestinal obstruction, deep vein thrombosis, pulmonary embolism, urethral fistula, urinary obstruction, perineal and lower extremity edema, and so forth. In our study, wound infection was seen in three patients (one in ligation group and two in non-ligation group) who had history of underlying diseases. Among them, two had type Ⅱ diabetes and one had hypertension, with insignificant difference between groups. Intestinal obstruction was seen in one patient of ligation group and one of non-ligation group; both of them were obese and did not start on-bed exercise early after operation; they stopped anus ventilate and defecating and experienced symptoms such as

abdominal distention at ten days after operation and were thus given X-ray examination, which suggested intestinal obstruction. Symptoms were relieved after symptomatic and supportive treatments. Post-operative fever was seen in two patients of ligation group and three of non-ligation group, probably caused by the absorption of drainage. No lower extremity deep vein thrombosis, pulmonary embolism or urethral fistula was seen in both groups. Therefore, we believed that lymphatic vessel ligation during operation would not increase the risk for wound infection, intestinal obstruction, fever and urinary obstruction after operation.

In the ligation group of our study, 11 patients had perineal and low extremity edema, of which ten had received post-operative pelvic radiotherapy; as for non-ligation group, 11 patients had perineal and lower extremity edema, of which ten had received post-operative pelvic radiotherapy. No significant difference was seen between them. Pelvic radiotherapy induced fibrosis or even closure of superficial subcutaneous lymphatic vessels and impacted lymph drainage, leading to edema at the drainage blockage sites.[13] Scholz et al.[9] reported that lymphoedema after pelvic lymphadenectomy generally lasted for three months (averagely 14.2 weeks). Patients who needed post-operative pelvic radiotherapy had all completed radiotherapy at the 12-week follow-up visit, therefore it was difficult to tell whether perineal and lower extremity edema was caused by radiotherapy or lymphatic vessel ligation. In our study, only five patients who did not receive radiotherapy had perineal and lower extremity lymphoedema after operation. The sample size was too small to provide answer to this question, which should be further explored by collecting a group of patients who did not need post-operative adjuvant radiotherapy.

Therefore, ligation of deep inguinal lymph vessels, proximal and distal obturator lymph vessels, common iliac lymph vessels, and the lymph vessels at the crossing of the external and internal iliac veins during pelvic lymphadenectomy is effective in reducing short-term occurrence of pelvic lymphocyst after operation, without increasing the occurrence of post-operative complications.

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