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ORIGINAL RESEARCH

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FloSeal for preventing symptomatic lymphocele after pelvic and/or para-aortic lymphadenectomy in gynecological cancers: a randomized controlled trial

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Abstract

To evaluate the role of FloSeal for preventing symptomatic lymphocele following pelvic and/or para-aortic lymphadenectomy in patients with gynecological cancers. Between October 2014 and April 2015, 40 patients with gynecological cancers planned for surgical management were randomly placed into FloSeal and non-FloSeal groups in a 1:1 ratio. Lymphocele incidence was evaluated using intravenous contrast-enhanced, abdominopelvic computed tomography 3–6 months after surgery. The quality of life questionnaire was completed by patients at 1, 3 and 6 months after surgery. The incidence of symptomatic lymphocele was compared using a chi-square test. All patients underwent bilateral pelvic lymph node dissection, and eight patients in each group (40% *vs.* 44.4%, $p > 0.999$) underwent para-aortic lymph node dissection. The mean number of total, right pelvic, left pelvic and para-aortic lymph nodes retrieved was similar between the groups. One patient (1/20, 5%) in the FloSeal group and three (3/18, 16.7%) in the non-FloSeal group developed lymphoceles ($p = 0.328$). The incidence of symptomatic lymphocele was 0% and 11% (2/18) in the FloSeal and non-FloSeal groups ($p = 0.218$), respectively. The mean time interval to drain removal (4.8 $\pm$ 2.0 days *vs.* 5.3 $\pm$ 2.2 days, $p = 0.400$) was shorter and the mean drain volume (1656 $\pm$ 1362 mL *vs.* 2022 $\pm$ 2301 mL, $p = 0.550$) was smaller in FloSeal group. The use of FloSeal after pelvic and/or para-aortic lymphadenectomy in patients with gynecological cancers may be effective for preventing symptomatic lymphocele. Clinical Trial registration: NCT01679483.

Keywords

Lymphocele; Lymphocyst; Lymphadenectomy; Lymph node dissection; Gynecological cancer; FloSeal

1. Introduction

Lymph node dissection is an important component of surgical staging and treatment of gynecological cancers, including uterine cervical, uterine corpus, ovarian and fallopian tube cancers. The most frequently reported postoperative complication of lymph node dissection is lymphocele (also known as lymphocyst) or lymphatic ascites (also known as chylous ascites). Among patients who have had a lymph node dissection for gynecological cancers, lymphocele or lymphatic ascites occurs in 57% patients [1–7]. Lymphoceles may compromise the quality of life of patients and delay adjuvant chemotherapy or radiotherapy following surgical intervention. Lymphoceles are also associated with secondary infections, and they may cause thromboembolic events because of the compression of pelvic veins. In addition, patients with postoperative lymphocele have a significantly higher chance of reintervention [8]. For these reasons, many techniques have been used to decrease the incidence of lymphocele and lymphatic ascites following lymph node dissection [9–12]. However, none of the previous techniques decreased the incidence of complications. Recently a prospective, randomized, pilot study including 60 patients with gynecological cancer found that a collagen patch coated with human coagulation factors decreased the incidence of lymphocele by 22% [6]. However, it was a surgical patch, which makes it difficult to apply in laparoscopic surgery. Because most gynecological cancer surgery is performed laparoscopically, further study is required for the use of materials that can be applied for this technique. FloSeal (Baxter Healthcare, Deerfield, IL, USA) is a hemostatic matrix paste composed of a bovine-derived gelatin matrix and human-derived thrombin that facilitates application during minimally invasive surgery. A Recent study found that the use of FloSeal effectively decreased the incidence of lymphocele by 12% [13]. Therefore, occluding open lymphatic channel following lymph node dissection using Floseal may decrease the incidence of lymphocele and lymphatic ascites. The aim of this study was to evaluate the role of FloSeal for preventing

symptomatic lymphocele following pelvic and/or para-aortic lymphadenectomy in patients with gynecological cancers.

2. Materials and methods

2.1 Patients

Patients with histologically confirmed primary cancer of the uterine cervix, uterine corpus, ovary and fallopian tubes and scheduled for surgery (*e.g.*, pelvic and/or para-aortic lymph node dissection) were eligible for this study. The International Federation of Obstetrics and Gynecology (FIGO) stages for the cancers in patients were as follows: IA2–IIA2 for cervical cancer, I–III for uterine corpus cancer, and I–IIIB for ovarian and fallopian tubal cancer. American Society of Anesthesiology Physical Status (ASA PS) ranged between 0 and 1, and the Eastern Cooperative Oncology Group (ECOG) performance status was between 0 and 2. Patients with uncontrolled medical disease that contraindicates primary surgery, including pelvic and/or para-aortic lymph node dissection, were not eligible. Patients who received chemotherapy or radiotherapy in the pelvis and/or abdomen before surgery were not eligible. Other inclusion and exclusion criteria are listed in **Supplementary Table 1**.

2.2 Study design

Randomization was performed using the blocked method with an equal allocation between the two treatment groups, using a stratification method according to the surgical method (*i.e.*, laparoscopy *vs.* laparotomy) and disease entity (*i.e.*, uterine cervical cancer *vs.* uterine corpus cancer *vs.* ovarian or fallopian tube cancer). Double-blinding was performed on the patients and surgeon until the completion of the study and lymph node dissection was complete. Therefore, randomization results were given to the surgeon at the completion of lymph node dissection before using the FloSeal.

Both laparoscopic and laparotomic approaches were permitted for surgical intervention. Lymphadenectomy was performed as previously reported [14–16], and it commenced in the right pelvis. After incision of the peritoneum covering the external iliac vessels, the lymph nodes surrounding the external iliac vessels were removed from the circumflex iliac vein to the bifurcation of the common iliac vessel while preserving the genitofemoral nerve on the psoas muscle. The obturator nerve and vessels were identified by retracting the external iliac vessels and isolating the obliterated umbilical artery. Afterward, the lymph nodes around the obturator and internal iliac vessels were removed. Moreover, left pelvic lymph node dissection was performed using the same method. If para-aortic lymph node dissection was indicated, lymphadenectomy was extended into the common iliac lymph nodes around the iliac vessels. After incision of the peritoneum covering the aorta and inferior vena cava, the ureters were identified and displaced laterally. Right para-aortic lymph nodes around the aortocaval, precaval and paracaval area were removed between the aortic bifurcation and origin of the right ovarian vein. Moreover, the left para-aortic lymph nodes were removed between the aortic bifurcation and the left renal vein.

In the FloSeal Group, two vials of Floseal were applied to each lymph node area at the completion of the lymph node dissection. The lymph node area was classified into three areas: (1) right pelvic lymph node area; (2) left pelvic lymph node area; and (3) para-aortic lymph node area (in cases in which para-aortic lymphadenectomy was performed). FloSeal was evenly applied on the entire area of each lymph node areas, and then compressed for 5 min using dry gauze and fingers (in the case of laparotomic surgery) or laparoscopic forceps (in the case of laparoscopic surgery). Excess FloSeal material was not incorporated into the hemostatic clot, and was removed by gentle irrigation according to the manufacturer's instructions. In the non-FloSeal group, nothing was applied to the lymph node area. All surgical procedures for the non-FloSeal group were the same as the FloSeal group, except that Floseal was not applied to the non-FloSeal Group.

After completion of the surgery, the peritoneum is usually left open and two available closed drain systems (*e.g.*, JP drain or Hemovac) were inserted into the right and left side of the pelvic cavity in most of the cases to lower the incidence of lymphocele formation with secondary infection in the closed retroperitoneal space. The drain system could be removed if the total drain amount was decreased to $<$500 mL/d at the discretion of the surgeon. Any documented adverse event within 30 days after surgery was recorded and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). After surgery, if adjuvant therapy was required, chemotherapy, radiotherapy or concurrent chemoradiotherapy was administered.

The EORTC (European Organisation for Research and Treatment of Cancer) Core Quality of Life questionnaire (EORTC QLQ-C30) was used to assess the patient's physical, psychological and social functions.

2.3 Follow-up and assessment

Intravenous contrast-enhanced, abdominopelvic computed tomography (APCT) was performed 3–6 months after surgery. If symptoms suggested lymphocele formation, APCT could be performed at any time point during the follow-up. The quality of life questionnaire (EORTC QLQ c-30) was filled out by patients at 1, 3 and 6 months after surgery.

2.4 Statistical analysis

This study was a pilot, double-blinded, randomized controlled trial. The study scheme is shown in Fig. 1. The primary endpoint of this study was the presence of lymphocele after lymphadenectomy.

Lymphocele was defined as round or ovoid fluid collection of any size in lymph node areas that recently developed after a lymphadenectomy. The incidence of lymphocele was compared using a chi-square test or Fischer's exact test. The mean values were compared using a Student's *t*-test. To evaluate the patients' quality of life (QOL), we evaluated the results of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, CX24 and OV28 in each visit; the data are summarized as the mean and standard error (SE) of QLQ-C30, CX24 and OV 28. The Linear mixed model was applied to test the effects of treatment and time and the interaction between treatment and

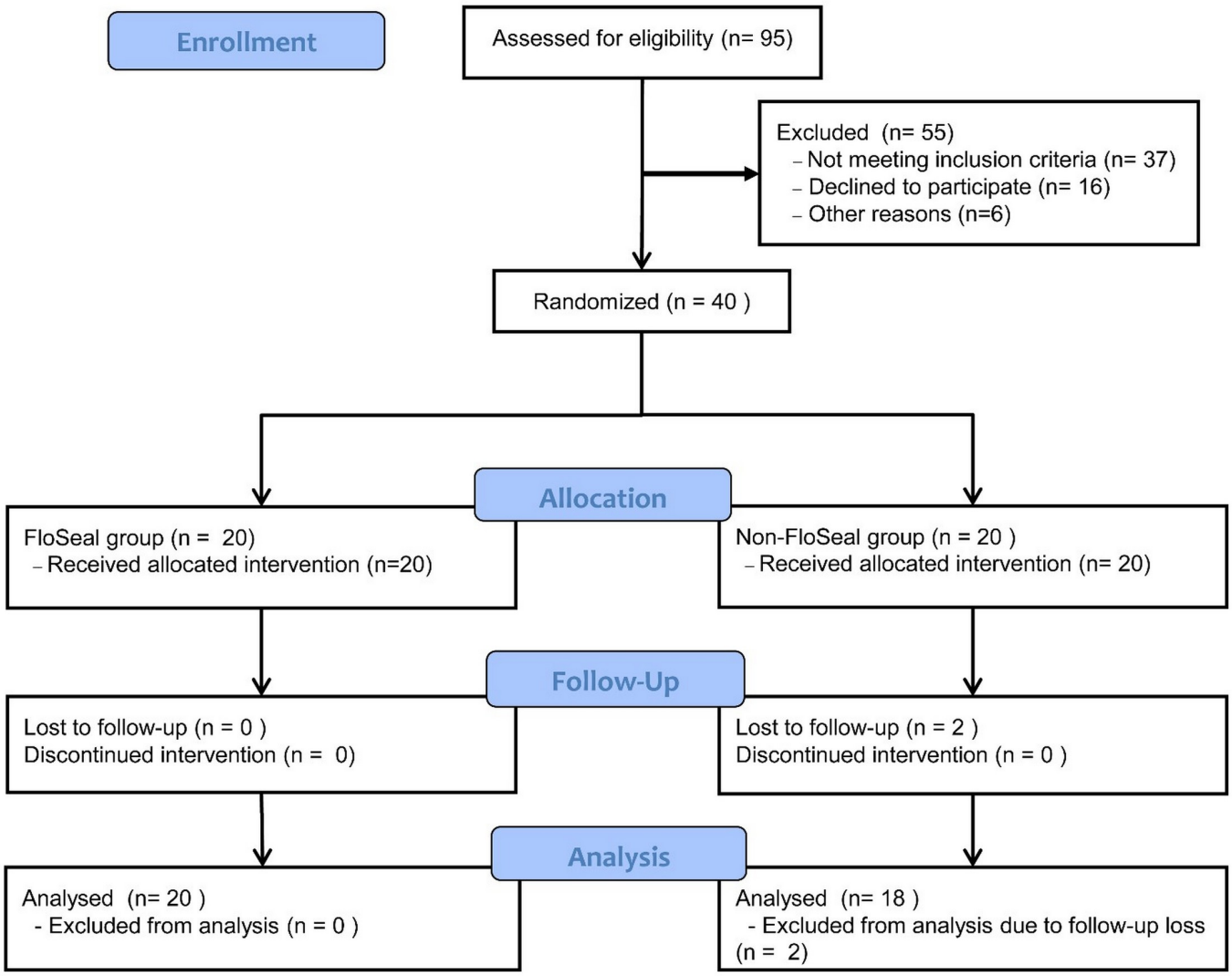

FIGURE 1. CONSORT form.

time for EORTC QLQ-C30, CX24 and OV 28, as well as its subdomains.

3. Results

From October 2014 and April 2015, 40 patients were randomized and received planned surgical intervention. However, two patients in the non-FloSeal group were lost to follow-up. The remaining 38 patients were included in the analysis. Table 1 presents the characteristics of patients. The FloSeal group had lower age distribution, and more patients in the FloSeal group were premenopausal. There was no difference in body weight, height, body mass index, parity, medical comorbidities, surgical history, the disease entity and surgical mode between the groups.

All patients underwent a bilateral pelvic lymph node dissection, and eight patients in each group (40% *vs.* 44.4%, $p > 0.999$) underwent para-aortic lymph node dissection together. The mean number of total, right pelvic, left pelvic and para-aortic lymph nodes retrieved did not differ between the FloSeal and non-FloSeal groups (Table 1). There was also no difference in the operating time (192 ± 57 min *vs.* 206 ± 70 min, $p = 0.488$), estimated blood loss (218 ± 152 mL *vs.* 199 ± 239 mL, $p = 0.791$), and transfusion requirement (1/20, 5% *vs.* 1/18, 5.6%, $p > 0.999$) between the FloSeal and non-FloSeal groups. Postoperative complications were reported in one patient (1/20, 5%) in the FloSeal Group, and three patients (3/18, 16.7%) in the non-FloSeal group ($p = 0.328$). One patient in the FloSeal group developed a febrile illness that subsided after the use of antibiotics. In the non-FloSeal group, two patients had febrile illness, and one patient suffered from febrile illness, atrial fibrillation, and postoperative hemorrhage. This patient underwent reoperation for hemostasis.

The mean time interval to drain removal (4.8 ± 2.0 days *vs.* 5.3 ± 2.2 days, $p = 0.400$) was shorter and the mean drain volume (1656 ± 1362 mL *vs.* 2022 ± 2301 mL, $p = 0.550$) was smaller in FloSeal group. Lymphocele developed in one patient (1/20, 5%) in the FloSeal group and three patients (3/18, 16.7%) in the non-FloSeal group ($p = 0.328$) (**Supplementary Table 2**). In the FloSeal group, one patient had only small (2.7 cm) asymptomatic lymphocele in left pelvis. However, in the non-FloSeal group, two out of three patients had symptomatic lymphocele. One patient (Patient 3) had a 16-cm infected lymphocele in the left pelvis, and was admitted for percutaneous drainage and intravenous antibiotics

TABLE 1. Patient characteristics of (n = 38).

		FloSeal group (n = 20)	Non-FloSeal group (n = 18)	*p* value
Age (yr)	Mean ± SD	47 ± 8.8	53 ± 9.5	0.029
Menopause, n (%)				
	No	14 (70)	6 (33.3)	0.024
	Yes	6 (30)	12 (66.7)	
Body weight (kg)	Mean ± SD	60 ± 8.2	58 ± 11.4	0.510
Height (cm)	Mean ± SD	158 ± 4.5	156 ± 6.6	0.267
Body mass index (kg/m^2)	Mean ± SD	24.28 ± 3.13	23.99 ± 3.98	0.807
Parity, n (%)				
	Nulliparous	4 (20)	2 (11.1)	0.663
	Parous	16 (80)	16 (88.9)	
Medical comorbidities, n (%)				
	No	16 (80)	14 (77.8)	>0.999
	Yes	4 (20)	4 (22.2)	
Surgical history, n (%)				
	No	9 (45)	14 (77.8)	0.052
	Yes	11 (55)	4 (22.2)	
Diagnosis, n (%)				
	Cervical Cancer	10 (50)	8 (44.4)	0.825
	Endometrial Cancer	8 (40)	7 (38.9)	
	Ovarian Cancer	2 (10)	3 (16.7)	
Surgical mode				
	Laparotomy	1 (5)	3 (16.7)	0.328
	Laparoscopy	19 (95)	15 (83.3)	
Lymph nodes retrieved, Mean ± SD				
	Total	37 ± 23.2	31 ± 16.2	0.381
	Right pelvic	16 ± 8.9	13 ± 6.1	0.197
	Left pelvic	15 ± 7.9	13 ± 6.0	0.245
	Para-aortic	6 ± 11.0	6 ± 9.1	0.955

SD: standard deviation.

(Fig. 2). Concurrent adjuvant chemoradiotherapy was stopped for 2 weeks during treatment of infected lymphoceles in this patient. The other patient (Patient 4) had a 12-cm lymphocele in left pelvis, and an 11-cm lymphocele in the para-aortic area (Fig. 3). However, no further treatment was performed for lymphocele because the patients did not want percutaneous drainage. Therefore, the incidence of symptomatic lymphocele was 0% and 11% (2/18) in the FloSeal and non-FloSeal groups (p = 0.218), respectively.

The QOL outcomes at baseline and each follow-up visit and QOL scores according to the time change are shown in **Supplementary Table 1**. Diarrhea items (DI) and attitude toward the disease and treatment items (AT) showed significant change according to the time change (Fig. 4).

4. Discussion

Lymphocele is one of the most problematic complications following lymphadenectomy in patients with gynecological cancers. To prevent symptomatic lymphoceles after lymphadenectomy, several surgical techniques and devices, including retroperitoneal drainage [4], peritonealization [17], omentoplasty [4] and the use of vessel sealing electrosurgical device [18, 19], as well as hemostatic agents and sealants (*e.g.*, fibrin glue [20], fibrin patch and a collagen-fibrin patch [6]) were evaluated in various studies. However, the efficacy of these biologic agents in preventing lymphatic complications remains unclear and there are limited studies on this matter. Retroperitoneal drainage, peritonealization and omentoplasty were not effective for preventing lymphocele [4, 17]. More-

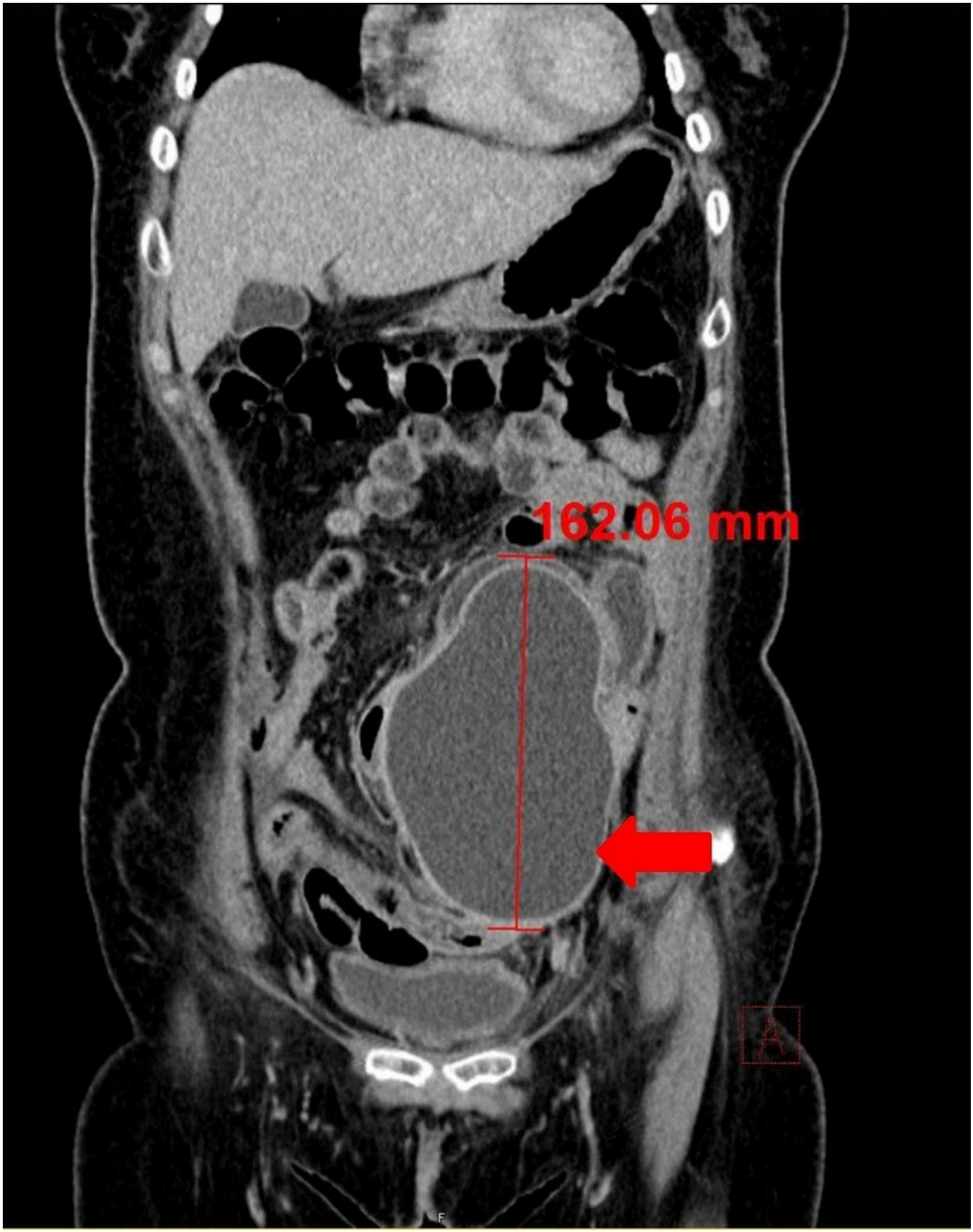

FIGURE 2. Symptomatic lymphocele in the Non-FloSeal group. This patient had a 16-cm infected lymphocele in the left pelvis (arrow), and was admitted for percutaneous drainage and intravenous antibiotics. Concurrent adjuvant chemoradiotherapy was stopped for 2 weeks during the treatment of the infected lymphocele.

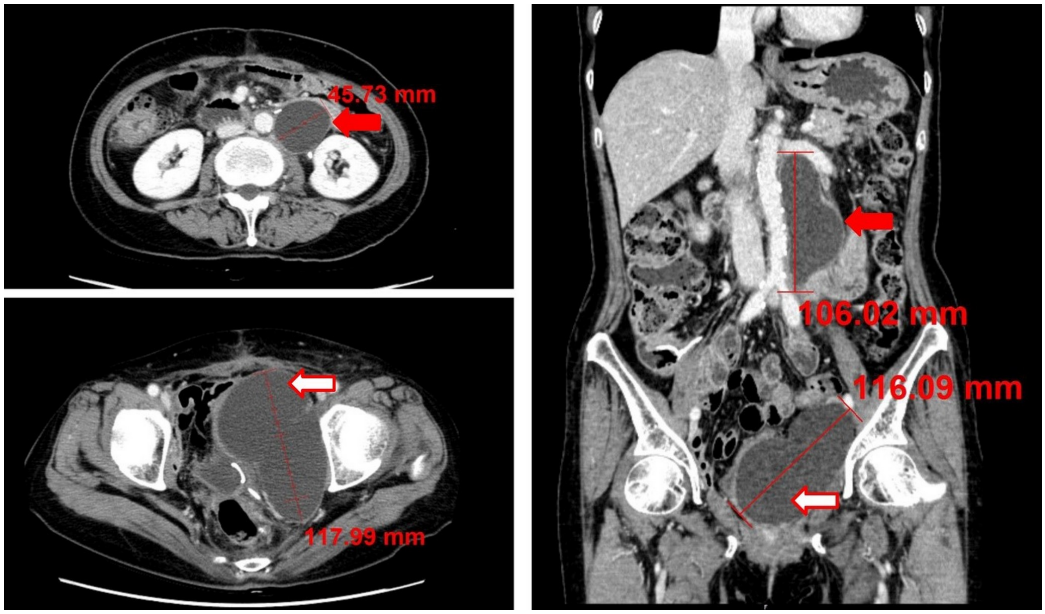

FIGURE 3. Symptomatic lymphocele in the Non-FloSeal group. This patient had 12-cm lymphocele in the left pelvis (open arrow), and an 11-cm lymphocele in the para-aortic area (arrow).

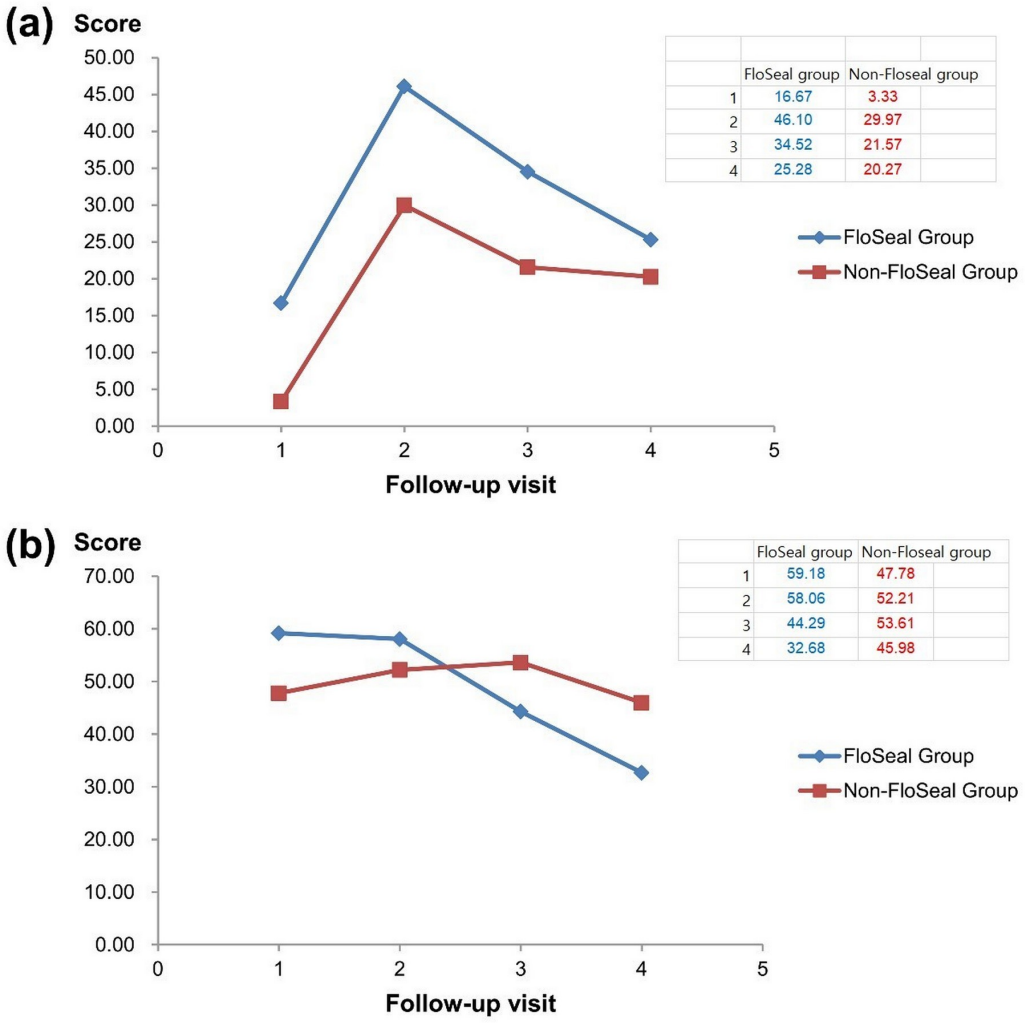

FIGURE 4. Changes in quality of life scores. (a) Diarrhea; and (b) attitude to disease and treatment. (Follow-up visit 1, 2, 3 and 4 are pre-operation, 1, 3 and 6 months after surgery).

over, the use of a vessel sealing electrosurgical device may completely occlude the lymphatics during lymphadenectomy. Recent randomized trials demonstrated that this is not effective for preventing lymphocele formation and is associated with an increased incidence of lymphedema following lymphadenectomy [18, 19]. Fibrin glue and sealants were also ineffective for preventing lymphocele after lymphadenectomy in patients with gynecological cancers in a randomized trial [11]. Recently a pilot, randomized trial found that the use of a collagen-fibrin patch is effective for preventing lymphocele formation after lymphadenectomy in patients with gynecological cancers [6]. Therefore, a large, randomized trial, including 140 patients with gynecological cancers was planned to evaluate the role of the collagen-fibrin patch in prevention of lymphocele [21]. However, the biomaterial type of the patch is difficult in the application of minimally invasive surgery and in covering a broad surgical field after pelvic and/or para-aortic lymphadenectomy as it is a solid material. FloSeal is a biomaterial liquid form paste and can thus be easily applied for minimally invasive surgery through narrow port hole; it can cover a broad area of the surgical field after pelvic and/or para-aortic lymphadenectomy. In a recent case-controlled pilot study, the use of FloSeal for laparoscopic lymphadenectomy in patients with gynecological cancers was shown to have a possible benefit for preventing lymphocele [22]. In that study, the incidence of lymphocele was lower in patients who received FloSeal without drainage than in patients who had drainage without FloSeal, following a pelvic and/or para-aortic lymphadenectomy (11% *vs.* 18%, $p = 0.454$). In addition, the postoperative hospital stay was shorter in the FloSeal group (6 days *vs.* 8 days, $p = 0.026$) [22]. In another matched study, the incidence of symptomatic lymphocele was lower in the FloSeal group than in the non-FloSeal group after laparoscopic or robotic pelvic lymphadenectomy (3.1% *vs.* 14.5%). The use of FloSeal following a lymphadenectomy was cost-effective in the cost analysis [13].

Our series was not without its limitations. A larger number of study patients could have overcome the age disparity between the 2 study subgroups which might have driven to more robust statistical analysis without lack of statistical difference. Also, the research time was long when considering the study size.

At the same time, our study is the first randomized trial evaluating the role of FloSeal for preventing lymphocele following pelvic and/or para-aortic lymphadenectomy especially in the minimally invasive surgery. No patients in the FloSeal group had symptomatic lymphoceles compared with two patients (2/18, 11%) in the non-FloSeal group. The difference in the symptomatic lymphocele incidence (11%) between the FloSeal and non-FloSeal groups in our study is similar to a previously matched study [13]. In our study, the mean numbers of the retrieved lymph nodes in the FloSeal and non-FloSeal groups were 37 and 31, respectively. Thus, we consider the lymph node dissection to be comprehensive. The optimal dosage of FloSeal for preventing lymphocele appears to be two vials for each lymph node area when we divided the lymph node areas into left pelvic, right pelvic, and para-aortic lymph node areas.

5. Conclusions

In conclusion, the use of FloSeal after pelvic and/or para-aortic lymphadenectomy in patients with gynecological cancers may be effective for preventing symptomatic lymphocele development.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

AUTHOR CONTRIBUTIONS

JYP and JHN—designed the research study. JYP, MHB and JHN—performed the research. JHN—provided help and advice on research details. JYP and MHB—analyzed the data. JYP—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was a pilot, prospective, randomized, controlled trial which was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea, and was registered at clinicaltrials.gov (identifier number: NCT01679483) before enrolling the first study subject. Written informed consent was obtained from all study subjects before study enrollment.

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This study was partly supported by the Baxter Healthcare, but it was not involved in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest. JYP is serving as one of the Editorial Board members/Guest editors of this journal. We declare that JYP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to LL.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1713786985953280000/attachment/Supplementary%20material.docx.

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