What Are the Risk Factors for Lymphocyst Formation Apart From Lymphnode Dissection and Lymphnode Count in Gynecologic Malignancy?

Was sind die Risikofaktoren der Lymphzystenbildung, abgesehen von der Lymphknotendissektion und der Lymphknotenanzahl in gynäkologischen Malignomen?

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Key words
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Abstract

Aim: Lymphocyst is one of the most common complications of lymphadenectomy and generally encountered during uro-gynecological oncology surgeries. We aimed to define the risk factors for formation of a lymphocyst in patients with various gynecological cancer types in whom a lymphadenectomy was performed.

Methods: This retrospective study was performed on 206 patients. Of the 206 patients, 100 were diagnosed with a lymphocyst, and 106 were assigned to a control group. Laboratory findings and surgical characteristics of the patients were compared.

Results: No differences were observed in age, pre-operative hemoglobin; platelet, white blood cell, and lymphocyte counts; or pre-operative albumin level ($p = 0.315$, 0.500, 0.525, 0.683, 0.740, and 0.97, respectively). A significant effect of the heparin dose × heparin days interaction and lymphocyst formation was observed ($p = 0.002$). Lymphocysts were most frequently detected in the ovarian cancer subgroup (49%). Significant differences were detected between the groups in the percentages of patients who underwent CT only and RT only treatments ($p = 0.001$ and 0.002, respectively). The logistic regression analysis revealed a relationship between the LMWH dose × days interaction and formation of a lymphocyst (OR, 1.10; 95% CI, 1.0–1.13; $p = 0.01$).

Conclusion: The association between total LMWH dose administered and the formation of lymphocysts in patients with gynecological pelvic cancer was investigated for the first time. Significant relationship between heparin dose × days and lymphocyst formation was found. Although anticoagulation with LMWH is essential for preventing thromboembolism, it should be used appropriately to prevent other complications, such as bleeding and lymphocysts.

Zusammenfassung

Ziel: Die Lymphzystenbildung ist eine der häufigsten Komplikationen nach einer Lymphadenektomie. Oft tritt sie im Rahmen von urogynäkologischen onkologischen Operationen auf. Ziel dieser Studie ist es, die Risikofaktoren für die Lymphzystenbildung bei Patientinnen mit verschiedenen gynäkologischen Karzinomtypen und durchgeführter Lymphadenektomie zu bestimmen.

Methoden: In die retrospektive Studie wurden 206 Patientinnen eingeschlossen. Bei 100 Patientinnen wurden Lymphzysten diagnostiziert, die übrigen 106 Patientinnen wurden der Kontrollgruppe zugeordnet. Laborbefunde und chirurgische Charakteristika beider Gruppen wurden verglichen.

Ergebnisse: Es wurden keine Unterschiede hinsichtlich des Alters, des präoperativen Hämoglobinwerts, der Thrombozyten-, Leukozyten- und Lymphozytenzahl oder des präoperativen Serum-Albumin-Werts festgestellt ($p = 0{,}315$, 0,500, 0,525, 0,683, 0,740 bzw. 0,97). Allerdings konnte ein signifikanter Effekt der Heparin-Dosis × Applikationsdauer auf die Lymphzystenbildung beobachtet werden ($p = 0{,}002$). Am häufigsten traten Lymphzysten bei Patientinnen mit Ovarialkarzinom auf (49%). Signifikante Unterschiede zwischen den Gruppen wurden auch hinsichtlich des prozentualen Anteils der Patientinnen beobachtet, die nur eine Chemotherapie oder nur eine Radiotherapie erhalten hatten ($p = 0{,}001$ bzw. 0,002). Die logistische Regressionsanalyse ergab eine Beziehung zwischen der LMWH-Dosis × Anwendungsdauer und der Lymphzystenbildung (OR, 1,10; 95%-KI 1,0–1,13; $p = 0{,}01$).

Folgerung: Zum ersten Mal wurde der Zusammenhang zwischen der verabreichten LMWH-Dosis und der Bildung von Lymphzysten bei Patientinnen mit gynäkologischen Malignomen untersucht. Es wurde ein signifikanter Zusammen-

hang zwischen der Heparin Dosis × Anwendungsdauer und der Lymphzystenbildung gefunden werden. Die Gabe von LMWH zur Antikoagulation ist zwar essenziell für die Prävention von Thromboembolien, sollte aber mit Vorsicht eingesetzt werden, um andere Komplikationen wie z. B. Blutungen und Lymphzystenbildung zu vermeiden.

Introduction

Pelvic lymphadenectomy is a common procedure for evaluating lymph node involvement in patients with gynecological cancer. Although this procedure provides important information, various complications, such as hemorrhage, increased operative time, and lymphocysts can occur [1]. Formation of a lymphocyst is one of the most common complications of lymphadenectomy [1]. A lymphocyst is a thick-walled cystic mass filled with lymphoid fluid that results from disruption of lymphatic channels and is generally encountered during uro-gynecological oncology surgeries or during the post-renal transplantation period [2–4]. Mori et al. reported formation of lymphocysts in 68 patients with cervical cancer who underwent lymphadenectomy in 1955 [5].

Although lymphocysts are generally asymptomatic and are found incidentally during postoperative follow-up, they may severely affect a patient's life by obstructing the ureter (hydronephrosis), bowel (ileus), or vessels (thrombosis), and they may become infected [3, 6–8]. Lymphocysts may also adversely delay treatment of the primary disease. The reported incidence of lymphocysts in patients undergoing gynecological cancer surgery is 1–58 % [3, 5–10]. The wide variation of the reported incidence might be explained partially by the presence of symptoms, type of surgical techniques used in treatment (laparatomy, laparoscopy, or robotic surgery) and diagnostic tools used for detection (ultrasonography, CT, or MRI). The data about the highest lymphocyst formation in which gynecological cancer occurs is scant and controversial. In a study by Kim et al. [8], the highest risk was reported to be in cervical cancer, whereas the highest rate was reported in ovarian cancer by Zikan et al. [10].

Various factors are associated with lymphocyst formation, such as the number of lymph nodes excised, lymph node involvement, surgical technique, anti-coagulant use, and postoperative radiotherapy (RT) and chemotherapy (CHT) [3, 7–11]. Although lymphocysts are the most common complication of lymphadenectomy, a limited number of studies have evaluated lymphocysts discovered during gynecological surgery. Most studies have been performed by urological and transplant surgeons, and the rest of the studies have controversial data about the risk factors. In order to prevent lymphocyst formation, several recommendations have been proposed such as drainage of resected sites, use of different energy sources for lymphadenectomy, non-closure of the peritoneum [3, 11].

In the present study, we evaluated and defined the risk factors for formation of a lymphocyst in patients with various gynecological cancer types in whom a lymphadenectomy was performed.

Materials and Methods

Study protocol

This retrospective case–control study was performed on 206 patients, who underwent surgery and were followed by the department of gynecological oncology at Izmir Tepecik Research and Training Hospital between January 2011 and March 2015 after Institutional Review Board approval. Of the 206 patients, 100 were diagnosed with a lymphocyst, and 106 were assigned to a control group. The control group patients were selected based on the ratio of retroperitoneal lymphadenectomy, number of pelvic (P) and para-aortic lymph (PA) nodes, and tumor histology type. Laboratory findings and surgical characteristics of the patients were obtained from medical records.

Management and follow-up of gynecological cancer in the local institution

Diagnosis and treatment of the gynecological cancers (endometrium cancer, cervix cancer, ovarian tumor, etc.) were performed according to our clinic guidelines. Management of endometrial cancer varied among practitioners, particularly with respect to the role of lymphadenectomy; no lymph nodes were sampled in some patients, only the P or PA nodes were sampled in other patients, complete staging with bilateral P lymph node dissection (LND) was applied in some patients, and some patients underwent complete staging with bilateral P and PA LND. The practitioners were responsible for these differences during the study. We performed retroperitoneal lymphadenectomy up to the renal vein or only harvested bulky lymph nodes in patients with ovarian cancer who underwent neoadjuvant CHT. We harvested P and PA lymph nodes to the level of the inferior mesenteric artery or common iliac bifurcation in patients with cervical cancer. Unipolar cautery and/or ligature were used to dissect the lymphatic tissues. Additionally, absorbable sutures or hemoclips were used to ligate lymphatic channels during dissection, if necessary. Intra-abdominal drains were placed if necessary to obtain early data about postoperative bleeding or leakage. Blood stopper was used in patients who underwent removal of P lymph nodes up to the left renal vein to evaluate whether blood stopper reduced the incidence of chylous acid (unpublished case–control study). No hemostatic or sealant agent, such as fibrin glue, was used after LND. Intra-abdominal drains were placed if necessary to obtain early data about postoperative bleeding or leakage.

Low-molecular weight heparin (LMWH) prophylaxis is started in our hospital 12 hours prior to surgery and continues until the patient is discharged or at postoperative week 3–4. The dose and duration of LMWH were calculated according to body mass index (BMI) and any patient risk factors (history of emboli, atrial fibrillation, or cardiovascular disease). We used dose (mg/kg) × duration (days) of prophylaxis to estimate the total dose administered, as this method provides more precise information than either dose or duration alone.

Patients with cervical cancer are typically seen in our clinic every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. Visits for patients with endometrial, ovarian, and fallopian tube cancers are scheduled every 3 months during the first year, every 4 months during the second year, every 6 months during years 3–5, and yearly thereafter.

Some of the patients were managed postoperatively with CHT alone, radiotherapy (RT) alone, or with both CHT and RT. RT was given as either external radiotherapy (ERT) alone, brachytherapy (IRT) alone, or ERT with IRT.

Diagnosis and diagnostic tools

The lymphocyst diagnosis was made based on findings of a fluid-filled cystic structure of varying shape, structure, and echogenicity (uni- or multi-locular, septated, etc.) as detected on trans-vaginal, trans-abdominal ultrasonography. The location, size in three dimensions (anteroposterior × transverse × caudal), shape (round or oval), echogenicity (hyper or hypo), and proximity to internal organs were evaluated by a radiologist who was an expert in gynecological ultrasonography. In cases of doubt or need for further details, computed tomography (CT) or *magnetic resonance* imaging (MRI) was ordered.

Statistical analysis

The χ^2 test and Student's t-test were used for the statistical analysis of unpaired data. A logistic regression analysis was conducted to determine factors affecting formation of a lymphocyst, and the results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed using MedCalc software ver. 11.5 for Windows (MedCalc Software, Inc., Ostend, Belgium). A p-value < 0.05 was considered significant.

Results

Demographic characteristics and laboratory findings of the groups

A total of 206 patients were analyzed, and 106 patients without lymphocysts were selected as the control group. The demographic and surgical characteristics of the groups are shown in **Table 1**. No differences were observed in age, pre-operative hemoglobin; platelet, white blood cell, and lymphocyte counts; or preoperative albumin level (p = 0.315, 0.500, 0.525, 0.683, 0.740, and 0.97, respectively). A significant effect of the heparin dose × heparin days interaction and lymphocyst formation (5.8 ± 5.58 in the control group, 10.3 ± 7.2 in the lymphocyst group) was observed (p = 0.002).

Results about the cancer types

Cancer types and their percentages are given in **Table 2**. No differences were found in cancer type between the lymphocyst and control groups (p = 0.058). Of the 100 patients with lymphocysts, 49 (49%) had ovarian cancer, 34 (34%) had endometrial cancer, 12 (12%) had cervical cancer, and 5 (5%) had uterine sarcoma. Lymphocysts were most frequently detected in the ovarian cancer subgroup (49%). The number of resected lymph nodes and positive lymph node counts are shown in **Table 3**. The numbers of P (22.2 ± 10.2 in the control group, 24.1 ± 11.3 in the lymphocyst group) and PA lymph nodes resected (15.0 ± 10.8 in the control group, 16.2 ± 11.1 in the lymphocyst group) and the numbers of positive P (0.8 ± 2.8 in the control, 1.0 ± 3.0 in the lymphocyst group) and PA lymph nodes (0.9 ± 2.9 in the control, 0.7 ± 2.1 in the lymphocyst group) were similar between the two groups (p = 0.228, 0.674, 0.416, and 0.584, respectively).

Results about the surgical techniques and other treatment modalities (CT & RT)

The types and statuses of the patient's surgeries and treatments (omental resection, pelvic drain, and administration of CHT only, RT only, or CHT and RT) in the two groups are shown in **Table 4**. Significant differences were detected between the groups in the percentages of patients who underwent CT only and RT only treatments (p = 0.001 and 0.002, respectively).

The logistic regression analysis

The logistic regression analysis revealed a relationship between the LMWH dose × days interaction and formation of a lympho-

Table 1 Demographic characteristics and laboratory findings of the control and lymphocyst groups.

Variable	Control group	Lymphocyst group	p-value
Age (years)	54.9 ± 10.6	55.9 ± 9.6	0.315
Preop. Hg*	11.8 ± 1.4	12.1 ± 1.3	0.500
Preop. WBC	7947 ± 2398	8091 ± 2259	0.525
Preop. Lymphocytes	2001 ± 738	2104 ± 870	0.683
Preop. Plt§	302600 ± 114602	301150 ± 110226	0.740
Preop. Albumin	2.8 ± 0.4	2.8 ± 0.4	0.197
LMWH€ (dose) × days	5.8 ± 5.58	10.3 ± 7.2	0.0001

* Preoperative hemoglobin, preoperative white blood cell count, § preoperative platelet count, € low molecular weight heparin

Table 2 Cancer types and ratios in the control group and lymphocyst group.

Cancer type	Control group	Lymphocyst group	p-value
Cervical	12 (11.3%)	12 (12%)	0.058
Endometrial	55 (51.9%)	34 (34%)	
Ovarian	34 (32.1%)	49 (49%)	
Sarcoma	5 (4.7%)	5 (5%)	

Table 3 Resected numbers (#) of pelvic lymph nodes (PLN)/para-aortic lymph nodes (PALN), and number of positive pelvic lymph nodes (PPLN)/positive para-aortic lymph nodes (PPALN) in the control group and lymphocyst group.

Lymph node type	Control group	Lymphocyst group	p-value
PLN	22.2 ± 10.2	24.1 ± 11.3	0.774
PALN	15.0 ± 10.8	16.2 ± 11.1	0.890
PPLN	0.8 ± 2.8	1.0 ± 3.0	0.514
PPALN	0.9 ± 2.9	0.7 ± 2.1	0.375

Table 4 Relationships between various factors (status of omentum resection, pelvic drains, and chemo/radiotherapy [CHT/RT] administration) and lymphocyst formation.

	Control group n (%)	Lymphocyst group n (%)	p-value
Omentum resection	48 (45.3%)	52 (52%)	0.403
Drain	92 (86.8%)	95 (95%)	0.110
CHT only	25 (23.6%)	46 (46%)	0.001
RT only	45 (42.5%)	23 (23%)	0.002
CHT and RT	23 (21.7%)	20 (20%)	0.449

Table 5 Logistic regression analysis of the risk factors.

Variables	Odds ratio	95% confidence interval	p-value
Albumin	1.5	0.6–4.0	0.32
LMWH dose × days	1.10	1.0–1.13	0.01
Cancer type	1.3	0.8–2.0	0.26
Omentum resection	1.15	0.5–2.3	0.68
# PLN	1.0	0.9–1.0	0.48
# PALN	1.0	0.95–1.0	0.54
# PPLN	1.0	0.8–1.2	0.66
# PPALN	1.1	1.0–1.4	0.36
CHT/RT	1.1	0.3–3.8	0.90
CHT only	1.7	0.5–5.7	0.32
RT only	2.1	0.6–7.1	0.32
Preop. lymph	1.5	0.8–1.5	0.35
Preop. plt	1.0	0.9–1.0	0.97

LMWH, low molecular weight heparin; PLN, pelvic lymph node; PALN, para-aortic lymph node; PPLN, positive pelvic lymph node; PPALN, positive para-aortic lymph node; CHT/RT, chemo and radiotherapy; CHT, chemotherapy alone; RT, radiotherapy alone; lymph, lymphocyte count; plt, platelet count.

cyst (OR, 1.10; 95% CI, 1.0–1.13; p = 0.01) (**Table 5**). However, the significant relationship between the RT only and CT only treatments and lymphocyst formation disappeared in the logistic regression analysis (OR, 2.1; 95% CI, 0.6–7.1; p = 0.32; OR, 1.7; 95% CI, 0.5–5.7; p = 0.32, respectively).

Discussion

Lymphocysts, which are also called lymphoceles or cystic masses filled with lymph, are primarily detected after a renal transplantation or urological and gynecological surgery that includes excision of lymph nodes [3, 11]. It is one of the most common complications of lymphadenectomy. Although lymphocysts are generally asymptomatic, they adversely affect treatment and may make patients and surgeons anxious.

The incidence of lymphocysts varies between 1 and 58% [3, 5–10]. The wide reported variation is probably due to different surgical techniques (laparatomy, laparoscopy, or robotic surgery) and diagnostic modalities used for detection (ultrasonography, CT, or MRI).

Several risk factors have been associated with lymphocyst formation, including BMI, gynecological cancer type, lymphadenectomy type (P or PA), number of positive lymph nodes, and surgery type (laparatomy, laparoscopy, or robotic surgery) [3, 8, 10–11]. However, data regarding these risk factors are controversial, and a very limited number of prospective clinical trials have evaluated them.

Kim et al. [8] reported that the highest lymphocyst formation rate was found in patients with cervical cancer, whereas Zikan et al. [10] reported the highest incidence in patients with ovarian cancer. Zikan et al. indicated that the difference is due to the complexity of the surgery performed to treat ovarian cancer. Although a difference was detected among the ovarian, endometrial, and cervical cancer subgroups in the incidence of lymphocyst formation, it was not statistically significant. As in the study by Zikan et al., the highest incidence we found was in patients with ovarian cancer, which may have been due to the greater number of lymph nodes removed and the difficulty of the surgery in these patients.

Data about the relationship between RT and lymphocyst formation are controversial [3, 8, 10–11]. Kim et al. [8] reported a higher incidence of lymphocysts in patients who received RT, whereas Zikan et al. [10] and Achouri et al. [11] reported no association between RT and an increased incidence of lymphocysts. In the present study, a significant relationship was found between RT and the development of lymphocysts, but the significance disappeared in the logistic regression analysis. Thus, controversy continues with regard to positive lymph nodes removed and the formation of lymphocysts. Although Zikan et al. [10] and Petru et al. [9] reported a significant relationship between positive lymph nodes and formation of lymphocysts, Achouri et al. [11] found no relationship between the number of positive lymph nodes and formation of lymphocysts. We also did not detect any relationship.

Several recommendations have been proposed to prevent lymphocysts, including non-closure of the peritoneum, an open-vaginal vault, drainage of resected sites, use of different energy sources for lymphadenectomy, and postoperative use of octreotide [3, 11].

The omentum protects the peritoneal cavity and plays a role in the turnover of peritoneal fluid, which has been assumed to be effective for preventing lymphatic complications and formation of lymphocysts. Several studies have evaluated the role of the omentum in preventing the formation of lymphocysts in patients with endometrial cancer. However, the sample sizes in these studies were very small (n = 22 and 64) [12–13]. We found no difference in the rate of lymphocyst formation in patients who did and did not undergo omentectomy.

Although drains have been recommended, despite the lack of evidence for their role in preventing formation of lymphocysts, and data about their effects are controversial [3, 8, 11]. In the present study, we found no association between drain placement or the number of drains and lymphocyst formation.

Most studies about lymphocyst formation and risk factors for their formation have been performed by urologists, and some possible risk factors have not been investigated in gynecological cases, such as heparin use. The association between use of LMWH and formation of lymphocysts has been investigated in several urological studies [14–15]. Sogani et al. reported that the incidence of lymphocysts was 19 times higher in patients who used prophylactic heparin compared with that in a control group [15]. However, Schmitges et al. evaluated the effect of LMWH on lymphocyst formation in patients who underwent prostatectomy and found no association between lymphocyst formation and heparin use [14]. Heinz et al. investigated the role of fibrin glue on the formation of lymphocysts in 47 patients with gynecological cancers [16], and reported no association between duration of heparin administration and lymphocyst formation. However, their study was designed to investigate the effect of fibrin on lymphocyst formation and did not report the dose or type of heparin used. In the present study, we found a significant relationship between heparin dose × days and lymphocyst formation. LMWH probably increases the risk for lymphocysts by altering tissue hemostasis after removing lymph nodes. The combination of the dose selected and duration of LMWH use may have an effect on lymphocyst formation.

The retrospective nature of the present study was the biggest limitation. Although, control group patients were selected randomly in order to prevent any bias, there are still differences within and between the groups with regards to cancer types, surgical and treatment types. Despite to these limitations, we investigated various risk factors that have not been fully evaluated previously, such as drains, omental resection, and CHT/RT, as well as factors that have not been investigated in patients with gynecological cancers, such as use of LMWH.

Conclusion

In the present study, the association between total LMWH dose administered and the formation of lymphocysts in patients with gynecological pelvic cancer was investigated for the first time. Although anticoagulation with LMWH is essential for preventing thromboembolism, it should be used appropriately to prevent other complications, such as bleeding and lymphocysts. A risk estimate analysis should be performed on prophylactic heparin use and the formation of lymphocysts in further randomized multicenter clinical studies.

Conflict of Interest

None.

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