Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A collagen-fibrin patch for the prevention of symptomatic lymphoceles after pelvic lymphadenectomy in women with gynecologic malignancies: A randomized clinical trial☆

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HIGHLIGHTS

- A collagen-fibrin patch does not reduce the rate of postoperative symptomatic lymphoceles.
- A collagen-fibrin patch does not reduce the rate of postoperative asymptomatic lymphoceles.
- Median lymphocele diameter is not reduced by the application of a collagen-fibrin patch.
- No independent risk factor for the development of lymphoceles was ascertained.

ARTICLE INFO

Article history:
Received 25 November 2017
Received in revised form 8 January 2018
Accepted 13 January 2018
Available online xxxx

Keywords:
Collagen-fibrin patch
Tachosil®
Lymphocele
Pelvic lymphadenectomy
Gynecologic malignancy

ABSTRACT

Objective. To evaluate the efficacy of a collagen-fibrin patch for the prevention of symptomatic lymphoceles after pelvic lymphadenectomy in women with gynecologic malignancies.

Methods. In a multicenter, randomized, clinical trial, 164 women with pelvic lymphadenectomy were allocated either to bilateral pelvic application of two collagen-fibrin patches or no intervention. Main outcome was efficacy, defined as reduction of symptomatic lymphocele rate diagnosed within four weeks after surgery. Secondary outcomes were asymptomatic lymphoceles and subsequent interventions. Sample size was based on the assumption that application of a collagen-fibrin patch reduces the prevalence of symptomatic lymphoceles by at least 66%. The study was single-blinded, i.e., patients and primary outcome assessors, but not surgeons, were blinded to the treatment allocation.

Results. A total of 75 women were randomized to the intervention and 89 to the control group. All women received the allocated intervention. In total, 42 (27.4%) lymphoceles and 8 (5.2%) symptomatic lymphoceles were observed. Symptomatic lymphoceles were observed in 5/68 (7.4%) women in the intervention group and 3/85 (3.5%) women in the control group ($p = 0.47$). Asymptomatic lymphoceles were observed in 16 (23.5%) women in the intervention group compared to 18 (21.2%) in the control group ($p = 0.85$). In a multivariate logistic regression model, no independent risk factor for the development of a symptomatic lymphocele was ascertained.

Discussion. Intraoperative application of collagen-fibrin patches to the pelvic side walls does not reduce the incidence of symptomatic lymphoceles in women with gynecologic malignancies undergoing pelvic lymphadenectomy.

☆ This study is registered at ClinicalTrials.gov (NCT01470677, protocol ID: TACHO-1) and the EudraCT database (EudraCT number: 2011-003115-34). Results were presented at the ESGO biannual meeting in Vienna 2017.

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https://doi.org/10.1016/j.ygyno.2018.01.012
0090-8258/

1. Background

Women with gynecologic malignancies such as cervical, endometrial, and ovarian cancer routinely undergo pelvic lymphadenectomy based on tumor characteristics assessed prior to or during surgery. Pelvic lymphadenectomy may be performed by open surgery or laparoscopy [1–4]. The rate of intraoperative complications during and after laparoscopic and open pelvic lymph node dissection is generally low, but has potential long-term consequences such as lower extremity lymph edema, nerve injury, and chronic pain [1–6].

In contrast, pelvic lymphoceles are considered a rather common event after pelvic lymphadenectomy [7]. In a recent meta-analysis, the prevalence of lymphoceles after pelvic lymphadenectomy varied between 23% and 63% [8]. This wide range in prevalence might be at least partially explained by the fact that most of the postoperative lymphoceles are asymptomatic and can only be detected by ultrasound or another imaging technique [4,5,7,8]. Therefore, underreporting in retrospective trials without defined follow-up protocol seems likely. In contrast to asymptomatic lymphoceles, symptomatic lymphoceles present a less common event. The largest study in women with gynecologic malignancies detected symptomatic lymphoceles in 5.8% after lymphadenectomy [7]. Of note, symptomatic lymphoceles are a severe postoperative complication frequently leading to medical and/or surgical interventions [7]. Additionally, symptomatic lymphoceles may delay adjuvant chemotherapy or radiotherapy.

A variety of interventions have been evaluated to reduce the rate of postoperative pelvic lymphoceles [8–11]. In previous reports the use of a fibrin-collagen patch has shown promising results [4,5]. Tachosil®, a fibrin-collagen coated patch, has been licensed in 2004 in Europe for the support of surgical hemostatic interventions. The efficacy and safety of this patch has been demonstrated in patients undergoing liver resection, pulmonary lobectomy, and kidney tumor resection [12–14]. A randomized controlled trial in men with prostate cancer undergoing pelvic lymphadenectomy observed significant reduction of sonographically detected lymphoceles as wells as reduced mean drainage volumes [4]. A single center, randomized controlled trial in women with endometrial cancer and pelvic lymphadenectomy found a similar reduction of lymphocele rates [5].

Of note, no randomized controlled trial investigated the efficacy of fibrin-collagen patches regarding a clinically relevant endpoint, i.e., symptomatic lymphoceles after pelvic lymphadenectomy. Thus, we performed a multicenter, randomized, single-blinded, clinical trial assessing the efficacy of a collagen-fibrin patch to prevent symptomatic lymphoceles in women undergoing pelvic lymphadenectomy for gynecologic malignancies. We hypothesized that the application of a collagen-fibrin patch will reduce the number of symptomatic pelvic lymphoceles after pelvic lymphadenectomy in gynecologic malignancies. In addition, we aimed to identify risk factors for the development of symptomatic and asymptomatic lymphoceles.

2. Patients and methods

In a multicenter, single-blinded, randomized, controlled, clinical trial, we included women with cervical cancer, endometrial cancer, and ovarian cancer undergoing pelvic lymphadenectomy. We hypothesized that the intraoperative bilateral application of two collagen-fibrin patches (Tachosil®) reduces the number of symptomatic pelvic lymphoceles by at least 66% (primary study endpoint). Sample size analysis was performed based on the data of Tinelli et al. [5]. In addition, we aimed to identify risk factors for the development of symptomatic and asymptomatic lymphoceles.

Institutional review board approval was obtained in all participating institutions. This study was registered at ClinicalTrials.gov (NCT01470677, protocol ID: TACHO-1) and at the EudraCT database (EudraCT number: 2011-003115-34). Moreover, the study protocol has been published previously [15]. The study consisted of two parallel groups with a 1:1 allocation ratio. No significant changes to the study protocol were made after study initiation [15]. In women randomized to the active group, two fibrin-collagen patches 4 × 8 cm in size were applied to the obturator fossa and around the external iliac artery and vein in both the right and left pelvic side wall. Women randomized to the control group received no fibrin-collagen patches. Analysis was performed by intention-to-treat. All patients signed an informed consent before surgery and study inclusion.

2.1. Outcome variables

The primary outcome variable was defined as follows: to evaluate the incidence of symptomatic pelvic lymphoceles defined by CTCAE 4.03 grade ≥ 2 within 4 weeks after surgery in women undergoing open or laparoscopic pelvic lymphadenectomy for cervical, endometrial, or ovarian cancer with and without the application of fibrin-collagen patches during surgery. The secondary outcome variables were defined as follows: (1) to evaluate the incidence of sonographically detected pelvic lymphoceles of at least 2 cm in the largest diameter 4 weeks after surgery; (2) to evaluate the rate and type of surgical and medical interventions for clinically symptomatic pelvic lymphoceles such as antibiotics, analgesics, lymphocele puncture and/or drainage, and surgery with removal or fenestration of a lymphocele; (3) to compare the rates of total and symptomatic lymphoceles between cervical, endometrial, and ovarian cancer patients, between patients with and without lymph node metastases, and between patients with open and laparoscopic pelvic lymphadenectomy; and (4) to evaluate the risk for total as well as symptomatic lymphoceles depending on the number of pelvic lymph nodes removed.

2.2. Randomization and study group allocation

Women were centrally randomized by one of the investigators (CT). Women were allocated to the application of fibrin-collagen patches (intervention group) or no intervention (control group) by blocks of 20 patients using a computer-generated randomization list for each study center. Using this list, allocation numbers were assigned and sealed in opaque envelopes with consecutive numbers for each center. The envelopes were sent to the respective study centers and were opened during surgery after completion of pelvic lymphadenectomy. The study was single-blinded, i.e., patients and primary outcome assessors, but not surgeons, were blinded to the treatment allocation. Outcome assessment was not performed by the surgeon, who had performed the lymphadenectomy and outcome assessors were not aware of the treatment allocation (observer-blinded).

2.3. Inclusion and exclusion criteria

Inclusion criteria were as follows: open or laparoscopic surgery for cervical, endometrial, or ovarian cancer including bilateral systematic pelvic lymphadenectomy, age between 18 and 70 years, and provision of written informed consent. Exclusion criteria were as follows: a history of previously diagnosed lymph edema, a known disease of the lymphatic system, presence or history of an immunosuppressive medication or a known disease of the immune system.

2.4. Study treatment procedures

All women underwent pelvic lymphadenectomy by open or laparoscopic surgery. The procedures were performed as follows: the peritoneum was incised parallel to the iliac vessels. Then, the iliac vessels were screened for the presence of bulky lymph nodes. If a lymph node debulking was performed, no fibrin-collagen patches were applied. In women with routine pelvic lymphadenectomy, lymph node tissue was removed from the external iliac vessels, the obturator fossa, the interiliac region, and the common iliac region after identification and

Please cite this article as: C. Grimm, et al., A collagen-fibrin patch for the prevention of symptomatic lymphoceles after pelvic lymphadenectomy in women with gynecologic malig..., Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.01.012