Gynecologic Oncology 134 (2014) 556–560

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Synthetic cyanoacrylic glue in the prevention of post-operative lymphocele after pelvic lymphadenectomy in patients with uterine malignancies: A prospective, single-blind, preliminary study

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HIGHLIGHTS

- The most frequent post-operative complication associated to lymph node dissection is lymphocele or lymphocyst.
- The use of synthetic glues has been proposed to reduce the creation of lymphocele.
- The synthetic cyanoacrylate glue reduces the incidence of lymphocele after pelvic lymphadenectomy in patients with uterine malignancies.

ARTICLE INFO

Article history:
Received 1 May 2014
Accepted 15 June 2014
Available online 23 June 2014

Keywords:
Lymphocele
Pelvic lymphadenectomy
Cyanoacrylate glue
Uterine malignancies
Post-operative complications
Lymphorrea

ABSTRACT

Objectives. Lymphoceles are among the most common post-operative complications of pelvic lymphadenectomy, with a reported incidence of 1% to 29% in gynecology oncology. Several studies evaluated the effectiveness of biological glues on reducing lymphoceles, but no data on gynecological patients are available. We evaluated the effectiveness of cyanoacrylic glues (n-butyl cyanoacrylate) (Glubran 2 — GEM s.r.l., Italy) in preventing lymphocele on 30 patients who underwent pelvic lymphadenectomy for endometrial or cervical cancer.

Methods. Single-blind prospective randomized study. Patients were divided into 2 groups: pelvic lymphadenectomy plus n-butyl cyanoacrylate (treatment group: 44 patients) and pelvic lymphadenectomy without n-butyl cyanoacrylate (control group: 44 patients). Primary endpoint was incidence of pelvic lymphocele in the two groups 30 days after surgery, and evaluated with pelvic ultrasound and RMI examination. Secondary endpoints evaluated drainage volume of lymphorrhea 36, 48, 72 and 96 h after surgery.

Results. 15% in the treatment group and 36.6% in the control group had lymphocele 1 month after the procedure ($p < 0.03$; RR 0.4 [95% CI 0.152–0.999]). Concerning the secondary outcome in group A the amount of lymphorrhea presented a constant significant decrease during evaluation; on the contrary, in group B, after an initial decrease at 48 h, the amount of lymphorrhea remained unchanged; at all considered times the amount of lymphorrhea resulted significantly greater in controls.

Conclusion. Intraoperative application of n-butyl cyanoacrylate seems to reduce lymph production after pelvic lymphadenectomy, providing a useful additional treatment option for reducing drainage volume and preventing lymphocele development after pelvic lymphadenectomy.

Introduction

Pelvic lymphadenectomy is an established step in the surgical staging and treatment of many gynecologic malignancies. Indeed, the surgical excision of metastatic nodes is considered to be both a pivotal diagnostic instrument and a debulking procedure.

Despite improvements in magnetic resonance imaging and positron-emission tomography for diagnosing lymph node involvement [1,2], histological examination of the lymphadenectomy specimens is the only reliable means of determining whether the nodes are involved by the neoplasia [3–5]. The therapeutic benefits of lymphadenectomy are controversial, and the complications of this procedure must therefore be carefully evaluated [6]. The most frequent post-operative complication associated with lymph node dissection is lymphocele or lymphocyst, with a reported incidence in gynecological oncology ranging from 1% to approximately 50% [7]. Lymphocele is a collection of lymphatic fluid along the lymphatic vessels, as a consequence of surgical dissection; the lymph accumulates in a pocket lined by epithelial tissue fibrosis

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http://dx.doi.org/10.1016/j.ygyno.2014.06.015
0090-8258/

[1]. Lymphoceles are common and occasionally symptomatic when they compress the surrounding structures and cause pelvic pain, hydronephrosis, deep vein thrombosis, infection, or sepsis [8]. Frequently, adjuvant radiotherapy is delayed or absolutely contraindicated in the presence of lymphoceles. Thus, this complication may interfere with the post-operative therapeutic protocol.

A number of techniques to reduce the incidence of post-operative lymphocele have been studied, including the non-closure of the pelvic peritoneum, omentoplasty, fibrin application, or the absence of retroperitoneal drainage [2,9–13], but none of these procedures has been demonstrated to be fully effective.

The use of synthetic glues as a means to reduce the creation of lymphocele has been proposed in the last years [14,15]. Among these, cyanoacrylate glue has marked hemostatic and adhesive properties. The glue in contact with the living tissue and a humid environment, acts rapidly creating a thin elastic film which guarantees a solid adhesion of the tissues. It starts to solidify after 1–2 s, finishing the reaction of solidification after 60–90 s. N-butyl cyanoacrylate glue is eliminated by a process of enzymatic degradation.

We performed a preliminary randomized trial to assess the impact of a cyanoacrylic glue on the incidence of lymphocele after pelvic lymphadenectomy in patients with uterine malignancies.

Material and methods

This was a preliminary, single-blind prospective randomized study performed at the Department of Gynecology and Obstetrics of the University of Naples Federico II.

From April 2011 to October 2012, all patients that would undergo systematic lymphadenectomy for gynecological malignancy (cervical or endometrial cancer) were included in the study. The inclusion criteria were: patients affected by cervical or endometrial cancer ≤stage 2 that are candidates to systematic lymphoadenectomy, expected survival ≥12 weeks, performance status ≥2, normal renal, hepatic and hemopoietic functions. The exclusion criteria were: ovarian malignancies, co-malignancies, previous radio- or chemotherapy, coagulation disorders, previous thromboembolic disease and previous lymphedema or lymphocele, which are contra-indications to surgical procedures or anesthesia.

The study has been approved by the Institutional Review Board of our Institution. The aim of the study was carefully explained to the patients before they participated in the study and their written consent was obtained.

The flow of patients throughout the study is illustrated in Fig. 1. Ninety-four patients satisfied the inclusion criteria, but six refused to undergo the randomization process and were excluded from the study. Eighty-eight patients were randomized into 2 groups in a 1:1 ratio by use of a randomization list generated by a computer with blocks of 6. Forty-four patients were scheduled to undergo planned surgical procedure including pelvic lymphoadenectomy with the use of cyanoacrylic glue (n-butyl cyanoacrylate) (Glubran 2 — GEM s.r.l, Italy) (treatment group), while 44 underwent planned surgical procedure including pelvic lymphoadenectomy without the use of cyanoacrylic glue (control group). The allocation sequence was concealed from the researchers (G.A.T.), who enrolled and assessed the participants and attached a sequentially numbered, opaque, sealed, and stapled envelope containing the allocated treatment to the clinical record of the patient after having signed the informed consent. The envelope was opened in the morning of the procedure. Patients were blinded to the procedure until the end of the study.

The following parameters were registered at baseline: age, weight, height and body mass index. For all patients, preoperative investigations included pelvic magnetic resonance or pelvic computerized tomography.

All procedures were performed by laparotomy by the same well-trained surgical team (C.N., G.B.). All patients underwent radical hysterectomy. In the case of endometrial cancer, women underwent type A radical hysterectomy with pelvic lymphadenectomy. Prophylactic antibiotics were administered intraoperatively. The first step of surgery was abdomino-pelvic washing, followed by radical hysterectomy, with or without bilateral annessectomy, and systematic pelvic lymphadenectomy. Systematic pelvic lymphadenectomy was started along the external iliac vein and proceeded inferiorly to the obturator fossa, to isolate and preserve the obturator nerve, the obturator artery and vein, and to

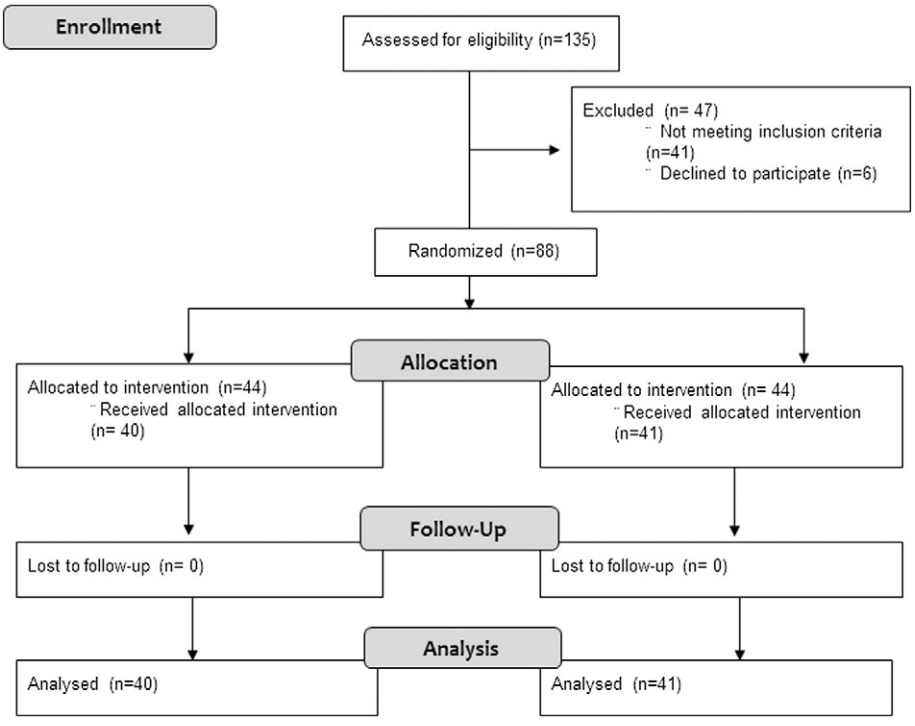

Fig. 1. The flow of patients enrolled in the study.