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F.N. Gilly[a]
Y. François[a, b]
A.C. Sayag-Beaujard[b, c]
O. Glehen[b]
A. Brachet[b]
J. Vignal[a, b]

[a] Department of Surgery, Centre Hospitalo-Universitaire Lyon-Sud, Pierre-Bénite,
[b] Laboratoire Recherche Oncologie, Université Lyon-1, Oullins, and
[c] Department of Anesthesiology, Centre Hospitalier Lyon Sud, Pierre-Bénite, France

Prevention of Lymphorrhea by Means of Fibrin Glue after Axillary Lymphadenectomy in Breast Cancer: Prospective Randomized Trial

Abstract

A prospective randomized trial was carried out to evaluate the efficacy of fibrin glue in preventing lymphorrhea after axillary lymphadenectomy in breast cancer. One hundred and eight breast cancer patients, operated on by two senior surgeons, were randomized into two groups: group 1 (n = 58) without fibrin glue and group 2 (n = 50) with 2 ml of fibrin glue applied to the axillary dissection area at the end of the lymphadenectomy procedure. Early postoperative morbidity was 2/58 and 0/50 in groups 1 and 2, respectively. Mean daily postoperative drainage was significantly greater in group 1. The mean cumulative drainage quantity 6 days after the operation was 407.8 ml and 214.4 ml in groups 1 and 2, respectively (p = 0.001). The mean postoperative hospital stay was 10.1 days and 8.0 days in groups 1 and 2, respectively (p = 0.006). One delayed seroma was observed in each group. Fibrin glue seems to reduce daily postoperative drainage and hospital stay, but did not affect delayed seroma formation after axillary lymphadenectomy for breast cancer.

Key Words

Fibrin glue
Lymphadenectomy
Breast cancer
Seroma

Introduction

Lymphorrhea is a common side effect after axillary lymphadenectomy for breast cancer in 15–45% of the cases [1]. Although uncomfortable, this complication does not carry any immediate danger to the patient. However, lymphorrhea means longer hospitalization and higher cost. Many surgical or core procedures have been proposed to decrease its incidence, such as the use of multiple drains, postmastectomy shoulder immobilization, external mammary artery preservation, but without success [2, 3].

To evaluate the ability of fibrin glue to prevent lymphorrhea after axillary lymphadenectomy in breast cancer, we decided to carry out a prospective randomized clinical trial after a pilot study [4].

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Prof. F.N. Gilly MD
Department of Surgery, CHLS
F–69495, Lyon Pierre-Bénite Cedex (France)
Tel. +33 4 78 86 13 75, Fax +33 4 78 86 33 43
E-Mail francogi@uheim.univ-lyon1.fr

Patients and Methods

Protocol

Between April 1995 and March 1996, a prospective randomized trial was carried out at the surgical department of the Centre Hospitalo-Universitaire Lyon-Sud. Inclusion criteria were: axillary lymphadenectomy for breast cancer, no previous irradiation, no previous chemotherapy and written informed consent. Only patients with previous axillary surgery were excluded.

After modified radical mastectomy (MRM) [5] or sector mastectomy (SM), lymphadenectomy was performed by two senior surgeons. A radical axillary lymphadenectomy, i.e. an axillary dissection extended to the three axilla levels [6], was done with sharp dissection and ligation of the larger and visible lymph vessels by titanium clips. Electrocoagulation was used as rarely as possible. The axillary vein was dissected over 6 cm, and the external mammary artery and vein were not preserved. At the end of the surgical procedure, randomization (sealed envelopes) into two groups was done: group 1 without fibrin glue and group 2 with fibrin glue (Tissucol®, Immuno, Vienna, Austria). Group 2 patients received 2 ml of Tissucol (with 3,000 IUK/ml aprotinin and 500 IU/ml thrombin concentrations) directly applied on the dissection area with a syringe, followed by a 2-min manual compression. In both groups, wound closure was carried out using separate stitches, and a vacuum drainage system was routinely used during the 6 postoperative days (drain placed in the axilla with a negative pressure of 21.5 kPa); all drains were removed after 6 days. A pressure bandage was applied for 2 days, and passive physiotherapy was performed from the 2nd to the 6th postoperative day.

During the immediate postoperative course, follow-up included a daily clinical examination (temperature curve, local status of the skin, general status of the patient) and measurement of the daily drainage and of the cumulative drainage over the first 6 postoperative days. Criteria for discharging patients were: not before the removal of the axillary drain, no fever (rectal temperature below 37.5 °C), no axillary wound inflammation, no seroma, decision of discharging made by a third surgeon not informed on the group of the patient. According to the protocol, a monthly postoperative examination of the patient was done over 6 months with close attention to the axillary area.

Patients

One hundred and eight patients with breast cancer (2 males, 106 females, mean age 60.1 years) were included in the study. Fifty-eight patients were randomized into group 1 (mean age 62.5 years, 11 MRM, 47 SM) and 50 patients were randomized into group 2 (mean age 60.6 years, 6 MRM, 44 SM). Characteristics of group 1 and group 2 patients are shown in table 1.

Statistical Analysis

All data were analyzed with a commercially available statistical program (SPSS 6.1, Chicago, Ill., USA). Data refer to mean and standard deviation. Student's t test, Mann-Whitney nonparametric test and the χ^2 test were used when appropriate for statistical analysis. Statistical significance was set at $p < 0.05$.

Results

Both groups were similar regarding age, weight, breast cancer staging, tumor differentiation, Scarff-Bloom and Richardson histological grading [7], number of removed lymph nodes and number of involved lymph nodes. They were no postoperative deaths.

Early postoperative morbidity was 2/58 in group 1: an 80-year-old woman, operated on by MRM for a $pT_2N_1M_0$ breast cancer had delayed wound healing until the 12th postoperative day, and a 56-year-old woman, operated on by SM for a $pT_2N_1M_0$ breast cancer, presented with a fever of 39 °C on the 2nd postoperative day (with sterile blood samples). Early postoperative morbidity was 0/50 in group 2.

Mortality and morbidity rates, mean daily drainage quantity in groups 1 and 2, as well as the 6-day cumulative drainage are shown in table 2.

The mean postoperative hospital stay was 10.1 days (2.1) in group 1 and 8.0 days (1.6) in group 2 ($p = 0.006$). Delayed complication rates were similar in group 1 (1/58) and in group 2 (1/50). In group 1, a 46-year-old woman, operated on by SM for a $pT_1N_1M_0$ breast cancer (6-day cumulative drainage = 240 ml), presented with a seroma on the 8th postoperative day; she was treated by 2 local aspirations

Table 1. Patient and tumor characteristics

	Group 1	Group 2	p value
Patients	58	50	
Age, years	62.5 (11.5)	60.6 (10.8)	0.456
Weight, kg	53.4 (9.6)	51.7 (10.1)	0.651
Surgical procedure			
MRM	11	6	
SM	47	44	
Tumor differentiation			
WD	24	22	
MD	30	27	
ND	4	1	
Scarff-Bloom and Richardson grading			
1	13	6	
2	35	32	
3	10	12	
Removed lymph nodes	10.8 (2.5)	10.6 (2.1)	0.744
Involved lymph nodes	1.9 (2.9)	1.9 (2.9)	0.940

Values are given in means (standard deviations are in parentheses).
WD = Well differentiated; MD = moderately and poorly differentiated; ND = undifferentiated.

Table 2. Perioperative data

	Group 1	Group 2	p value
Mortality	0/58	0/50	–
Morbidity	2/58	0/50	n.s.
Drainage day 1, ml	83.5 (53.1)	65.5 (32.8)	p = 0.03
Drainage day 2, ml	84.1 (35.0)	55.1 (24.9)	p = 0.05
Drainage day 3, ml	65.6 (39.4)	48.1 (29.7)	p = 0.01
Drainage day 4, ml	49.8 (34.9)	28.5 (21.9)	p = 0.05
Drainage day 5, ml	47.5 (40.5)	28.5 (22.6)	p = 0.04
Drainage day 6, ml	55.8 (47.5)	24.2 (19.7)	p = 0.02
6-day cumulative drainage, ml	407.8 (240.1)	214.4 (105.9)	p = 0.001

Values are given in means (standard deviations are in parentheses).
n.s. = No statistically significant difference.

(9th and 16th postoperative day) and was alive and well without axillary sequelae 14 months later. In group 2, a 71-year-old woman, operated on by SM for a $pT_2N_1M_0$ breast cancer (6-day cumulative drainage = 350 ml), presented with a seroma on the 14th postoperative day: she was treated by 3 local aspirations (14th, 19th and 27th postoperative day) and was alive and well without axillary sequelae 8 months later.

No other late complication was observed during the 6-month follow-up (no shoulder limitation, no arm edema, no delayed axillary infection).

Discussion

After axillary lymphadenectomy in breast cancer, postoperative seroma does not seem to be an alarming problem but remains the main cause for prolonged hospital stay and frequent visits to the outpatient clinic. It also increases the cost of health care.

Despite the common use of postoperative drainage with high- or low-vacuum drains [8], the risk persists. Another approach can be to glue together the wound surfaces after dissection, and the introduction of fibrin glue 15 years ago suggested new possibilities [9]. Nevertheless, no advantage could be shown in the use of fibrin glue after lymphadenectomy [10, 11]. Some studies reported a success in rat mastectomy models [12, 13], but only two human reports [4, 14] were able to reduce the incidence of seroma or daily drainage volume with fibrin glue after mastectomy.

From a physiological point of view, fibrin plays a central role in wound healing: it induces chemotaxis of polymorphonuclear granulocytes and promotes the initial inflammatory phase of the healing process [15].

The results we observed in the present study are similar to those reported in our pilot study [14]: the use of fibrin glue in axillary lymphadenectomy does not reduce the postoperative rate of seroma (1/58 in group 1 and 1/50 in group 2), but significantly decreases the postoperative daily drainage volume (table 2) as well as the postoperative cumulative drainage volume (407.8 ml in group 1, 214.4 ml in group 2, $p = 0.001$) and decreases the postoperative hospital stay (10.1 days in group 1, 8.0 days in group 2, $p = 0.006$). This decrease in postoperative hospital stay has to be carefully analyzed, as the day of drain removal in this study was preoperatively scheduled. From the present study, it was not possible to conclude whether decreasing daily drainage volume has a significant impact on seruma formation or not.

Disappointing results have been reported using fibrin glue following axillary lymphadenectomy [10, 11, 16, 17], but aprotinin and thrombin concentrations in the glue were different from the ones we used. The way of sealing the wound area was not the same (use of spray with an air pump and a 4-bar gas pressure). Use of high gas pressure with fibrin glue has been reported for liver hemostasis, but produced a layer which was too thin for lymphostasis in the context of axillary dissection. The use of a syringe where pressure is not important allowed the formation of a thick layer of fibrin glue and adhesion to the dissection area and subcutaneous tissues. As far as this adhesion is concerned, this was achieved by systematic manual compression for 2 min after application, followed by a pressure bandage after skin closure.

In other series, postoperative drainage durations are shorter but without any preoperative decision regarding duration of drainage: the 6-day drainage time we selected in this trial was long, and a similar prospective study could be done with a 2- or 3-day drainage, or even without any drainage. There continues to be controversial and conflicting evidence in the literature about how long drains should be left in and what the rate of seroma is in relation to early or late drainage removal [18].

It is to be emphasized that the surgeon's technique and experience as well as sharp and tissue-sparing dissection with ligation may be related to the quality of postlymphadenectomy results. In this trial, as far as the surgeon's technique is concerned, patients were operated on by the same two senior surgeons, both

using a standardized surgical protocol (no electrocoagulation except for subcutaneous tissues, extensive use of titanium clips, no blunt-finger dissection, use of immediate postoperative pressure bandage).

Conclusion

From the present prospective randomized trial, it can be concluded that the use of fibrin glue in axillary lymphadenectomy for breast cancer leads to a significant reduction in postoperative drainage volume, but does not affect delayed seroma formation. Further prospective trials will be useful to clarify the impact of fibrin glue on hospital stay after axillary lymphadenectomy.

Warning: In 1988, Tissucol has received marketing authorization in France, but users have to be aware of potential national prohibition. Users of fibrin glue have to contact the producer company to be sure whether the product is homologated in their own country or not.

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