

New trends on fibrin glue in seroma after axillary lymphadenectomy for breast cancer

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SUMMARY: New trends on fibrin glue in seroma after axillary lymphadenectomy for breast cancer.

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Background. Axillary lymphadenectomy remains an integral part of breast cancer treatment, yet seroma formation occurs in 15–85% of cases. Among methods to reduce seroma magnitude and duration, fibrin glue has been proposed in several studies with controversial results.

Patients and methods. Ninety patients underwent quadrantectomy or mastectomy with level I/II axillary lymphadenectomy; a suction drain was fitted in all patients. Fibrin glue spray were applied to the axillary fossa in 45 patients; the other 45 patients were treated conventionally.

Results. Suction drainage was removed between post-operative (p.o.) days 3 and 4. Seroma magnitude and duration were significantly reduced (p 0.004 and 0.02, respectively), and there were fewer evacuative punctures, in patients receiving fibrin glue compared with the conventional treatment group.

Conclusions. Use of fibrin glue does not always prevent seroma formation, but does reduce seroma magnitude, duration and evacuative punctures.

RIASSUNTO: Indicazioni attuali sull'impiego della colla di fibrina nei sieromi dopo linfettomia ascellare nel cancro della mammella.

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Introduzione. La dissezione ascellare rimane parte integrante del trattamento del cancro della mammella; la percentuale di sieromi è comunque abbastanza elevata (15–81%). Molte tecniche sono state proposte per ridurre la intensità e la durata dei sieromi. L'impiego della colla di fibrina è stato proposto in diversi studi con risultati controversi.

Pazienti e metodi. Sono state arruolate 90 pazienti con cancro della mammella sottoposte a quadrantectomia o mastectomia con linfettomia ascellare di I e II livello. È stato sempre posizionato un drenaggio aspirativo. In 45 pazienti è stata utilizzata colla di fibrina nel cavo ascellare.

Risultati. Il drenaggio aspirativo è stato rimosso tra la III e la IV giornata post-operatoria. L'entità e la durata del sieroma è stata inferiore (p 0.004 e 0.02, rispettivamente) con un minor numero di punture evacuative nel gruppo di pazienti trattate con colla di fibrina rispetto al gruppo di controllo.

Conclusioni. L'impiego della colla di fibrina non è in grado di prevenire la formazione del sieroma post-linfettomia ascellare ma ne riduce l'entità e la durata oltre che la necessità di punture evacuative.

KEY WORDS: Breast cancer - Seroma - Fibrin glue.
Cancro della mammella - Sierosa - Colla di fibrina.

Introduction

Axillary dissection represents an integral part of the treatment of breast cancer for prognostic and curative purposes. There is still a significant incidence (15–81%)

(1–5) of complications associated with axillary lymphadenectomy, including lymphorrhea, lymphoceles, and in rare cases lymphedema (swelling of the arm). It is possible to avoid axillary dissection in selected patients (T1 N0) using the sentinel lymph node technique. However, in all cases where $T > 3$ cm, and in patients with T1 N1 or with metastatic sentinel lymph node, conventional axillary lymphadenectomy remains an integral part of the primary surgical protocol for quadrantectomy and mastectomy.

Many different methodologies have been used to reduce seroma formation following axillary lymphadenectomy for breast cancer. These include suction drain-

Second University of Naples
General and Specialistic Surgery
¹ University of Perugia
General Endocrine Surgical Unit

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nage (6,7), topical application of tetracycline (8), closing and stitching the axillary fossa (9, 10), axillary dissection with axilloscopy (11), external compression (12, 13), and application of fibrin glue (14-16). To date, no practical guidelines exist about suction drainage, and the views of surgeons are different. Some surgeons believe that it is best to remove the drain on the first day of the post-operative period, some think the drain should be left in place until the drained volume falls below 50 ml/day (17), while others feel that drainage could in fact prolong and intensify the inflammatory stage of the wound-healing process, with a subsequent increase in seroma formation (18).

Regardless of contradicting opinions, the possibility of reducing the time of drainage during the postoperative period, eliminating the need to discharge patients with drainage *in situ*, may represent a valid solution for reducing seroma formation. This prospective study evaluates the effectiveness of using fibrin glue to reduce seroma formation following axillary lymphadenectomy for breast cancer.

Patients and methods

Between January 2006 and March 2008, 90 patients were enrolled in the study. All patients had N+ breast adenocarcinoma and required either quadrantectomy or modified radical mastectomy with level I or II axillary lymphadenectomy, extending from the lower border of the axillary vein superiorly and from the medial border of the smaller pectoral muscle medially, as far as the fourth intercostobrachial nerve inferiorly and to the edge of the latissimus dorsi laterally. For the axillary lymphadenectomy, the vascular-lymphatic branches were ligatured to limit the use of an electric scalpel.

To be enrolled in the study, patients were required to have: no alterations in their blood clotting or immune systems, or at least not be receiving anticoagulant treatment; have no history of sensitisation to bovine aprotinin; no psychological changes; no uncompensated diabetes or advanced liver disease; no severe obesity; and no previous surgery on the axillary lymphatic system or any immediate reconstructive surgery. Short-term antibiotic prophylaxis was applied.

The enrolled patients were divided into two randomized groups, each comprising 45 patients (30 quadrantectomies and 15 mastectomies). After surgery, all patients were fitted with a suction drain at the axillary fossa, which was activated 10 minutes after stitching the skin. One group (control group) received the suction drain without additional treatment, while the other group received fibrin glue.

For patients in the treatment group, following fitting of the drain, fibrin glue prepared with 500 IU/ml of thrombin was applied as a spray (2 ml, from a distance of 10 cm with 2 bars of pressure) at the site of the quadrantectomy or mastectomy. Fibrin glue prepared with 5 IU/ml of thrombin was also applied as a spray (2 ml) to the axillary fossa by approximately three minutes' manual compression. A compression dressing was applied over the treatment site and kept in place for at least 24-72 hours. Fibrin glue for the axillary fossa was prepared by diluting it to 5 IU/ml with calcium chloride solution (20 mM), a concentration capable of maintaining activation of the wound-healing process through a thick mesh of fibrin fibrils.

Patients were discharged when the volume drained fell below 100 ml/day and suction drainage could be removed. One week later, patients underwent clinical and instrumental (ultrasound) assessment for the presence of seroma, and any residue was suctioned out using an echo-guided evacuative puncture, as necessary. The primary outcome measures of the study were a) the incidence of seroma, including total volume of serum drained, and b) number of evacuative punctures required. A secondary outcome measure of the study was the duration of the treatment up to the time of healing. Complications associated with the axillary lymphadenectomy procedure were also recorded.

The Wilcoxon rank-sum test was used to assess differences between the two patient groups.

Results

Factors as age, size of tumor and its ratio to the residual breast volume following surgery, the number of lymph node removed and the number of metastatic lymph nodes did not represent significant variables in terms of seroma magnitude.

All patients were discharged 3-4 days following surgery. Two patient in the control group was discharged with the drain *in situ* because the serum volume was greater than 100 ml/day. The patients was controlled by family doctor at home and the drain was removed in days 7 and 8 p.o.

Compared with patients in the control group, patients in the fibrin glue group had a significantly lower drainage volume (120 [60-350] versus 250 [110-550] ml; $p = 0.004$), fewer evacuative punctures (2 [0-3] versus 4 [1-5]), and a significantly reduced mean seroma duration, i.e. healing time (11.2 [4-21] versus 17.5 (4-32) days; $p = 0.02$). The incidence of complications was 20% (8 cellulitis and 1 wound diastasis) and 28,8% (11 cellulitis and 2 wound diastasis) in patients who underwent surgery with and without fibrin glue, respectively. No significant relationship was observed in either patient group between the magnitude of seroma formation and the type of surgical procedure (quadrantectomy or mastectomy).

Discussion

Breast cancer surgery, in particular axillary lymphadenectomy, has changed in the last few years with the advent of the sentinel lymph node technique (11). However, even today there are a number of situations where a conventional axillary lymphadenectomy is indicated, including patients with tumours greater than 3 cm in diameter, with positive or suspect axillary lymph nodes at objective examination or instrumental imaging, or with a positive sentinel lymph node. In this group of patients, the axillary lymphadenectomy still has complications, in particular seroma formation (15-81%) (1-5),

which can delay the patient's discharge, healing and adjuvant radiotherapy and chemotherapy treatments.

The formation of seroma can result from a lesion of the axillary lymphatic vessels (2) or from an inflammatory reaction (18), which may also be prolonged and intensified by the suction drainage (19). The removal of drainage for some surgeons is indicated when the volume per day is less than 50 ml², but we prefer to remove the drainage when the volume per day is less than 100 ml, as in our experience drains do not prevent seroma formation, and they also dictate the date of discharge, resulting in a longer stay (3). A number of surgeons believe that it is possible to discharge patients with the drainage *in situ* (3), despite the associated discomfort and increase in percentage infection rate. This issue of drainage management at home arises in cases of procedures carried out in day surgery.

Many published articles on the usefulness of drainage following axillary lymphadenectomy contradict each another with regard to seroma control, magnitude and duration. Somers et al. (5) compared patients with or without drainage and found that there was greater incidence and degree of seroma, with longer duration, in patients without suction drainage. Porter et al. (20) reported non-significant difference in the incidence and degree of seroma between patients with suction drainage (73%) versus patients without suction drainage (89%). Divino et al. (6) reported 6% incidence of seroma for patients with drainage, compared with 40% for patients without. Petrek et al. (21) demonstrated a relationship between the magnitude of the seroma and lymph node positivity based on metastasis or earlier lymph node biopsies. Burak et al. (22) noted a relationship between seroma magnitude and patient age. Salmon et al. (23) reported a positive correlation between the incidence of seroma and size of the breast removed. Using ultrasound monitoring, Jeffrey et al. (24) reported 92% seroma incidence in patients without drainage, and sharing the view of others that repeated suction may be the cause of infections of the axillary fossa (25-26) using evacuative puncture only in symptomatic cases (42%).

To reduce seroma magnitude, there have been numerous reports of the benefits of using external compression dressing (27), immobilization of the arm (28), sutures to close the axillary fossa (29), excessive use of the electric scalpel compared with ligature of the lymphatic branches (20-30), multiple drains (21), different type of suction (high- or low-pressure) (31). The use of fibrin glue has also produced contrasting results: reduction of seroma according to Moore et al. (14) and Gilly et al. (32); and no difference in seroma formation compared with patients treated without fibrin glue, according to Burak et al. (22), Langer et al. (33) and Dinmore et al. (34). The latter authors attributed the lack

of benefit to the presence of drainage possibly interfering with the stabilization of a fibrin clot, and with closure of the lymphatic capillaries. Fibrin glue interacts with the tissues damaged during the surgical procedure, favoring the growth of fibroblasts and wound healing. It favors hemostasis by preventing hematomas, which delay the surgical healing processes; makes the lymphatic branches impermeable, reducing seroma formation; and makes it possible to close the dead spaces through tissue adhesion.

A number of papers have presented comparative studies of patients with and without fibrin glue in the axillary fossa. In a study of 24 patients who underwent quadrantectomy or mastectomy with axillary lymphadenectomy, Gioffre' Florio et al. (35) demonstrated that the use of fibrin glue reduced seroma magnitude. In a group of 186 patients, Tasinato et al. (36) reported a reduction in seroma magnitude, duration and the number of evacuative suction on patients on whom fibrin glue spray was used, compared with patients whose axillary fossa was only washed with povidone-iodine or saline solution. In a group of 20 patients who underwent quadrantectomy with axillary lymphadenectomy, Tirelli et al. (37) noted a reduction in the magnitude and duration of seromas in patients in whom fibrin glue was used. In a study involving 116 patients who underwent a surgical procedure of quadrantectomy or mastectomy with axillary lymphadenectomy, Jain et al. (38) reported a seroma incidence of around 40%, with a reduction in seroma magnitude in mastectomy patients in whom fibrin glue was used, although a significant difference was not observed between quadrantectomy patients treated with or without fibrin glue. The study demonstrated that suction drainage did not limit the incidence or magnitude of seromas, and that it was associated with extended time spent in hospital and post-operative pain. Yet in a study of 87 patients, Soon et al. (39) showed that, among patients who underwent quadrantectomy or mastectomy with axillary lymphadenectomy, there was no difference in terms of the incidence of seromas with or without the use of suction drainage, and that, for the group of patients without drainage, the seromas formed in greater magnitude and for a longer duration, but with a lower percentage of complications. Kuroi (40), in a meta-analysis of 51 randomized controlled trials, 7 prospective studies and 7 retrospective studies, showed that there was moderate evidence to support a risk for seroma formation in subjects with higher body weight, extended radical mastectomy and greater drainage volume in the first 3 days; with regard to the use of adhesive glue, many retrospective studies failed to show any significant effect on seroma formation.

Based on our experience, and reviewing data from the literature, it seems that the magnitude and duration

of the seromas are limited, but they are present in over 80% of patients, without significant differences between mastectomy and quadrantectomy. In our opinion the use of fibrin glue may therefore be useful in traditional breast

cancer surgery for reducing magnitude and duration of the seroma, and shortening the stay in hospital which, in this pathology too, is increasingly performed in day surgery.

References

1. Roses DF, Brooks AD, Harris MN et al. Complications of level I and II axillary dissection in the treatment of carcinoma of the breast. *Ann Surg* 1999;230:194-201.
2. Woodworth PA, McBoyle MF, Helmer SD, Beamer RI. Seroma formation after breast cancer surgery: incidence and predicting factors. *Am Surg* 2000;66:444-451.
3. Classe JM, Dupre PF, Francois T et al. Axillary padding as an alternative to closed suction drain for ambulatory axillary lymphadenectomy: a prospective cohort of 207 patients with early breast cancer. *Arch Surg* 2002;137:169-173.
4. Abe M, Iwase T, Takeuchi T et al. A randomized controlled trial on the prevention of seroma after partial or total mastectomy and axillary lymph node dissection. *Breast Cancer* 1998;5:67-69.
5. Somers RG, Jablon LK, Kaplan MJ et al. The use of closed suction drainage after lumpectomy and axillary node dissection for breast cancer: a prospective randomized trial. *Ann Surg* 1992;215:146-149.
6. Divino CM, Kuerer HM, Tartter PI. Drains prevent seromas following lumpectomy with axillary dissection. *Breast J* 2000;6:31-33.
7. Kopelman D, Klemm O, Bahous H, Klein R, Krausz M, Hasmónai M. Postoperative suction drainage of the axilla: for how long? Prospective randomized trial. *Eur J Surg* 1999;165:117-120.
8. Rice DC, Morris SM, Sarr MG et al. Intraoperative topical tetracycline sclerotherapy following mastectomy: a prospective, randomized trial. *J Surg Oncol* 2000;73:224-227.
9. Aitken DR, Hunsaker R, James AG. Prevention of seromas following mastectomy and axillary dissection. *Surg Gynecol Obstet* 1984;158:327-330.
10. O'Dwyer PJ, O'Higgins NJ, James AG. Effect of closing dead space on incidence of seroma after mastectomy. *Surg Gynecol Obstet* 1991;172:55-56.
11. Procaccini E, Ruggiero R, Falco P et al. La dissezione ascellare con tecnica mini-invasiva. *Tumori* 2003; Suppl 89:198.
12. Chaturvedi P, Chaturvedi U. Axillary compression with delayed drain removal reduces prolonged seroma formation. *J Surg Oncol* 2001;78:279-280.
13. O'Hea BJ, Ho M, Petrek JA. External compression dressing *versus* standard dressing after axillary lymphadenectomy. *Am J Surg* 1999;177:450-453.
14. Moore M, Burak Jr WE, Nelson E et al. Fibrin sealant reduces the duration and amount of fluid drainage after axillary dissection: a randomized prospective clinical trial. *J Am Coll Surg* 2001;192:591-599.
15. Dinsmore RC, Harris JA, Gustafson RJ. Effect of fibrin glue on lymphatic drainage after modified radical mastectomy: a prospective randomized trial. *Am Surg* 2000;66:982-985.
16. Berger A, Tempfer C, Harmann B et al. Sealing of postoperative axillary leakage after axillary lymphadenectomy using a fibrin glue coated collagen patch: a prospective randomized study. *Breast Cancer Res Treat* 2001;67:9-14.
17. Yii M, Murphy C, Orr N. Early removal of drains and discharge of breast cancer surgery patients; a controlled prospective clinical trial. *Ann R Coll Surg Engl* 1995;77:377-379.
18. Watt-Boolsen S, Nielsen VB, Jensen J, Bak S. Postmastectomy seroma. A study of the nature and origin of seroma after mastectomy. *Dan Med Bull* 1989;36:487-489.
19. Moher D, Schulz KF, Altman DG for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191-1194.
20. Porter KA, O'Connor S, Rimm E, Lopez M. Electrocautery as a factor in stroma formation following mastectomy. *Am J Surg* 1998;176:8-11.
21. Petrek JA, Peters MM, Cirrincione C, Thaler HT. A prospective randomized trial of single *versus* multiple drains in the axilla after lymphadenectomy. *Surg Gynecol Obstet* 1992;175:405-409.
22. Burak WE Jr, Goodman PS, Young DC, Farrar WB. Seroma formation following axillary dissection for breast cancer: risk factors and lack of influence of bovine thrombin. *J Surg Oncol* 1997;64:27-31.
23. Salmon R J, Cody HS, Verdrenne JB. Prevention des lymphocèles postopératoire après amputation du sein. *Press Med* 1985;14:27.
24. Jeffrey SS, Goodson WH III, Ikeda DM, Birdwell RL, Bogetz MS, Giuliano A. Axillary lymphadenectomy for breast cancer without axillary drainage. *Arch Surg* 1995;130:909-913.
25. Purushotham AD, McLatchie E, Young D et al. Randomized clinical trial of no wound drains and early discharge in the treatment of women with breast cancer. *Br J Surg* 2002;36:286-292.
26. Bundred N, Maguire P, Reynolds J et al. Randomised controlled trial of effects of early discharge after surgery for breast cancer. *BMJ* 1998;317:1275-1279.
27. O'Hea BJ, Ho MN, Petrek JA. External compression dressing versus standard dressing after axillary lymphadenectomy. *Am J Surg* 1999;177:450-453.
28. Dawson I, Stam L, Heslinga JM, Kalsbeek HL. Effect of shoulder immobilization on wound seroma and shoulder dysfunction following modified radical mastectomy: a randomized prospective clinical trial. *Br J Surg* 1989;76:311-312.
29. O'Dwyer PJ, O'Higgins NJ, James AG. Effect of closing dead space on incidence of seroma formation following mastectomy. *Surg Gynecol Obstet* 1991;172:55-56.
30. Miller E, Douglas EP, Morrisey K, Cortese A. Scalpel *versus* electrocautery in modified radical mastectomy. *Am Surg* 1988;54:284-286.
31. Van Heurn LW, Brink PR. Prospective randomized trial of high *versus* low vacuum drainage after axillary lymphadenectomy. *Br J Surg* 1995;82:931-932.

32. Gilly FN, Francois Y, Sayag Beaujard AC et al. Prevention of lymphorrhea by means of fibrin glue after axillary lymphadenectomy in breast cancer: prospective randomized trial. *Eur Surg Res* 1998;30:439-443.
 33. Langer S, Guenther M, Fronzo A. Does fibrin sealant reduce drain output and allow earlier removal of drainage catheter in women undergoing operation for breast cancer? *Am Surg* 2003;69:77-81.
 34. Dinsmore RC, Harris JA, Gustafson RJ. Effect of fibrin glue on lymphatic drainage after modified radical mastectomy: a prospective randomized trial. *Am Surg* 2000;66:982-985.
 35. Gioffre' Florio MA, Mezzasalma F, Manganaro T et al. L'impiego della colla di fibrina nella chirurgia del carcinoma della mammella. *Giorn Chir* 1993;14:239-241.
 36. Tasinato R, Godina M, Griggio L et al. Prevenzione della linforrea ascellare nelle pazienti sottoposte a linfadenectomia per carcinoma mammario. *Acta Chir Italica* 1993;49:479-484.
 37. Tirelli C, Pantano FP, Morucci R et al. I sieromi nella chirurgia mammaria. *Baxter* 2003.
 38. Jain PK, Sowdi R, Anderson DG, MacFie J. Randomized clinical trial investigation of the use of drains and fibrin sealant following surgery for breast cancer. *Br J Surg* 2004;91:54-60.
 39. Soon PSH, Clark J, Magarey CJ. Seroma formation after axillary lymphadenectomy with and without the use of drains. *Breast* 2005;14:103-107.
 40. Kuroi k, Shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S, Saito S . Evidence based risk for seroma formation in breast surgery. *Japanese Journal of Clinical Oncology* 2006;36:197-206.
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