

Effect of collagen powder on lymphorrhoea after modified radical mastectomy. A randomized controlled trial

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Summary

Aim: Postoperative lymphorrhoea is a major complication of axillary lymphadenectomy. The aim of our study was to evaluate the impact of type I collagen in postoperative lymphorrhoea in mastectomy patients. **Methods:** Eighty patients that underwent modified radical mastectomy for breast cancer were randomized in two groups. In group A (collagen group, n = 42) collagen type I (Cellerate RX powder) was applied in the axillary cavity after lymphadenectomy while in group B (control group, n = 38) lymphadenectomy was performed in the standard fashion without the use of a sealant. Suction drains remained in place until the daily amount of lymphatic drainage fell under 30 ml. The total amount and the duration of drainage, as well as the morbidity and severity of arm pain were compared in the two groups. **Results:** There was a non significant trend towards lower overall drainage in the collagen group. The duration of drainage and postoperative pain were similar in the two groups, as was morbidity. Subgroup analysis of patients according to the number of lymph nodes excised, revealed significantly less lymphorrhoea in terms of volume and duration in patients who had more than ten lymph nodes excised. **Conclusion:** Collagen type I (Cellerate RX powder) appears to attenuate postoperative lymphorrhoea in patients undergoing axillary lymphadenectomy especially when > 10 lymph nodes are removed.

Key words: Modified radical mastectomy; Lymphorrhoea; Collagen.

Introduction

Although it is considered a minor complication of breast surgery, prolonged lymphatic drainage after axillary dissection is the most common cause of long hospitalization for breast cancer patients, who usually have an otherwise uneventful postoperative course [1-4]. Breast surgeons employ many different techniques to achieve reduction of lymphorrhoea, like the use of ultrasonic scissors and fixation of skin flaps on the chest wall intraoperatively, or pressure dressings postoperatively [5-9]. In view of the insignificant results of all these methods and having in mind the known action of collagen as a biologic sealant, we tested the effect of type I collagen powder (Cellerate RX, Wound Management Technologies, Inc, USA) on the volume and duration of lymphorrhoea in patients with modified radical mastectomy.

Patients and Method

Between 2004 and 2009 we conducted a prospective randomized trial evaluate the impact of collagen type I on axillary drainage after lymphadenectomy. Eighty female patients were enrolled in the study and underwent mastectomy for breast cancer and axillary lymph node dissection level I-II. Exclusion criteria were: A) previous operations on the axilla, B) neo-adjuvant chemotherapy, C) previous chest wall irradiation, D) immediate breast reconstruction, and E) recurrent disease.

After informed consent, each patient was randomized to receive either type I collagen (collagen group) or nothing (control group) in the axillary cavity. Randomization was performed using a web based program. All patients were offered

modified radical mastectomy using electrocautery for the breast excision and blunt dissection along with ligation of lymphatics and vessels in the axilla. They were all treated with axillary node dissection level I-II, since sentinel lymph node biopsy had not yet been established as standard of care in our institution at the time of the study. Type I collagen powder (Cellerate RX) was used in the collagen group (42 patients). Three grams of powder were applied on the exposed tissue in the axillary cavity and the mastectomy flaps, after the completion of lymphadenectomy. Before skin closure two soft suction drains (Jackson-Pratt) were used – one for the axilla and one on the chest wall. The wound was covered with simple dressings. Starting from postoperative day 1 each patient was encouraged to use her arm and follow a program of special exercises for arm mobilization. Drainage was monitored on a daily basis and the drain was removed when it fell under 30 ml/day. Monitoring was performed by experienced hospital personnel that was blinded to the treatment assignment. All patients remained hospitalized until the removal of the drains to ensure that monitoring was reliable. The daily amount of drainage was the total volume of axillary and chest wall drainage. Total amount of drainage consisted of the amount in the drains and the amount of serous fluid aspirated, in case of seroma.

On the first and third postoperative day both groups were asked to assess the severity of pain in the ipsilateral arm using a visual analogue scale.

The primary endpoints of the study were the duration and the volume of drainage, and the secondary endpoint was the severity of the pain in the arm and the morbidity in the two groups of patients.

Seroma was defined as a palpable serous collection in the axilla that needed aspiration. Wound infection was defined as erythema of the wound accompanied by collection, and was treated with aspiration and the appropriate antibiotics after wound cultures.

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Statistical analysis was performed using SPSS software. Quantitative data were expressed as mean values and the comparison between the two groups was made using the Student's t-test. A *p* value < 0.05 was considered statistically significant.

Results

All 80 patients enrolled completed the study. There were no significant differences between the two patient groups (collagen vs control group) with regards to age, body mass index, number of lymph nodes removed and disease stage (Table 1).

The mean overall drainage output for collagen group was 507 ± 85ml (mean value ± SD) versus 693 ± 100 ml for the control group. The mean duration of drainage was 5.2 ± 1.1 days for collagen group versus 6.8 ± 1.2 days for controls (Table 1). Although these results showed a non significant difference between the two groups, there was a trend towards lower output and shorter duration of drainage in the collagen group. Postoperative pain measurements on days 1 and 3 were not statistically significant in the two groups (Table 1). The complication rate was similar in both groups. With regard to seromas, the incident and the total volume aspirated showed no statistically significant difference in the two groups. The same was true for wound infection (Table 1).

According to the number of lymph nodes excised, patients were classified into two subgroups: subgroup A included 24 patients with ten or fewer lymph nodes excised whereas subgroup B included 56 patients with more than ten lymph nodes excised. An additional statistical analysis was performed for these subgroups and the results are demonstrated in Table 5. For subgroup A, the use of collagen on the axilla had no impact either on the overall amount or on the duration of drainage (520 ± 75 ml versus 643 ± 65 ml and 5.2 ± 1.5 days versus 5.8 ± 2 days). For subgroup B, the effect of the use of collagen was statistically significant and reduced both the amount and the duration of lymphorrhea (Table 2). Further subgroup analysis based on lymph node status showed no difference in the amount and duration of drainage in patients with positive or negative lymph nodes.

Discussion

Although breast surgery is known to have only a few and usually minor complications, prolonged lymphorrhea after axillary dissection is very common. Patients who develop this complication are not only obliged to retain their drains and eventually stay hospitalized for several days, but they are also prone to developing further problems, like seroma, wound infection or even lymphosarcoma [1-3].

Lymphorrhea is attributed to both an acute inflammatory reaction resulting from the surgical stress and to the transaction of lymphatics during axillary dissection. When it seizes a few days (3-4) after surgery it is a well accepted postoperative event that is not regarded as a complication [6-8]. On the contrary, prolonged lymphatic

Table 1. — Comparison between the collagen and control group regarding patient characteristics, volume and duration of postoperative drainage, and severity of postoperative pain using the Visual Analogue Scale and complications.

	Collagen group n = 42	Control group n = 38	<i>p</i>
<i>Preoperative data</i>			
<i>Patient characteristics</i>			
BMI (kg/m ²)	24 ± 2.5	23 ± 3.2	NS
Age (years)	65 ± 3.1	62 ± 5.2	NS
LN excised	12.5 ± 4.1	11.2 ± 3.4	NS
Positive LN	3 ± 2.2	3 ± 2.7	NS
<i>Postoperative data</i>			
<i>Drainage</i>			
Overall (ml)	507 ± 85	693 ± 101	NS
Duration (days)	5.2 ± 1.1	6.8 ± 1.2	NS
<i>Postoperative pain (mm)</i>			
day 1	76	83	NS
day 3	23	25	NS
<i>Complications</i>			
Seromas	8	10	NS
Seroma volume (ml)	150 ± 30	167 ± 20	NS
Wound infection	3	2	NS
Total	11	12	NS

BMI: Body mass index, LN: lymph nodes, Values expressed in mean ± SD.

Table 2. — Correlation between lymphatic drainage and number of excised lymph nodes in the two groups.

	≤ 10 lymph nodes excised			> 10 lymph nodes excised		
	Collagen group	Control group	<i>p</i>	Collagen group	Control group	<i>p</i>
<i>Preoperative data</i>						
Patients	12	12		30	26	
Overall drainage (ml)	520 ± 75	643 ± 65	NS	495 ± 85	743 ± 75	0.040
Drainage duration (days)	5 ± 1.5	5 ± 2	NS	7 ± 3	11 ± 4	0.030

Values expressed in mean ± SD.

drainage is a rather unpleasant situation caused by certain pathophysiologic mechanisms [3, 7, 8]. The fibrinolytic activity of the plasmin system in serum and lymph may contribute to fluid accumulation and fibrin complexes, that have already formed within and around vessels, may become degraded resulting in further leakage [1]. Bonemma *et al.*, report that seromas do not contain enough fibrinogen, resulting in impaired coagulation [2].

Factors predisposing to prolonged postoperative lymphorrhea are old age, obesity, preoperative chemotherapy and high axillary dissection, while timing of mobilization and type of drains are not important [3-5]. A number of different surgical techniques have been employed to reduce the incidence of lymphorrhea, e.g., the use of ultrasound scissors instead of electrocautery, the fixation of flaps with sutures on the thoracic wall, the placement of full or half vacuum suction drains or the use of pressure dressings [6-8]. Many authors have tried fibrin sealant or tetracycline in the axillary cavity and others used subcutaneous octreotide [9-11].

In our study we used porcine hydrolysate collagen type I (Cellerate), that is known to promote and accelerate cellular regeneration by replicating the natural fibroconnec-

tive template. It works by attaching to fibroblasts to the wound bed forming a biologic platform that encourages the healing process. All 60 patients enrolled in the protocol had similar characteristics and the surgical technique was the same. It is noteworthy that all patients underwent modified radical mastectomy and they all followed the same program for arm mobilization, so that the postoperative drainage could be comparable. Although there was no statistically significant effect on the total volume and duration of lymphorrhea between the two groups, there was a trend towards improved outcomes in the collagen group. Subgroup analysis of patients classified according to the number of lymph nodes removed revealed the beneficial effect of collagen. Total amount and duration of drainage was statistically significant in the subgroup of patients that had more than ten lymph nodes excised. This finding is of major clinical importance in the era of therapeutic-only lymphadenectomy for breast cancer. It is widely accepted that complete axillary dissection and axillary sampling as staging procedures for early breast cancer have already been replaced by sentinel lymph node biopsy. Therefore, lymphadenectomy should only be performed for therapeutic reasons either in case of a positive sentinel lymph node for early cancer patients or as a standard treatment for advanced cancers, and many centers around the world advocate even level-III clearance. The minimum accepted number of lymph nodes excised in this case should be at least ten. In this setting, the clinical importance of the beneficial effect of collagen in this specific subgroup of patients is significantly reinforced. Our study included cases of both therapeutic and staging lymphadenectomy, as sentinel lymph node biopsy had not yet been established in our unit at the time of the study.

However, further complications attributed to lymphorrhea, such as postoperative seromas and wound infection, as well as arm pain were not affected by the use of collagen. Our results are in accordance with other studies that report decreased lymphorrhea with no impact on delayed seroma formation and other complications [12-14]. On the other hand, several trials with a small number of patients failed to prove the protective effect of sealants. In addition, a systematic review concluded that there is no strong evidence to support the use of fibrin in axillary surgery [15-17].

Conclusion

Based on our results, the use of type I collagen reduces the overall amount and duration of postoperative lymphorrhea in patients undergoing modified radical mastectomy with standard therapeutic lymphadenectomy and excision of more than ten lymph nodes avoids prolonged hospitalization. However, it does not affect postoperative morbidity and pain.

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