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ORIGINAL ARTICLE – BREAST ONCOLOGY

Effectiveness of OK-432 (Sapylin) to Reduce Seroma Formation After Axillary Lymphadenectomy for Breast Cancer

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ABSTRACT

Background. The occurrence of seroma formation after axillary lymphadenectomy for breast cancer cannot be ignored. Various approaches have been used in an effort to reduce it, but these results are still controversial. We aimed to describe a new method of application of OK-432 (Sapylin, heat-treated Su strain of *Streptococcus*) to reduce seroma formation after axillary lymphadenectomy for breast cancer and to verify the safety and efficacy of it as a beneficial supplement for conventional surgery.

Methods. A prospective, randomized analysis of consecutive quadrantectomy or mastectomy plus axillary lymphadenectomy using or not using OK-432 was designed. From July 2010 to November 2011, a total of 111 patients were enrolled in this prospective, randomized study and completed the follow-up. OK-432 applied to the axillary fossa plus placement of closed suction drainage was used in 54 patients (the experimental group); placement of closed suction drainage was used in 57 patients (the control group).

Results. There were no statistical significance between the two groups in terms of age, body mass index, treatment received, tumor size, number of removed lymph nodes, and lymph node status. Postoperative drainage magnitude and duration were significantly reduced in the experimental group ($P = 0.008$ and 0.003, respectively). One week after hospital discharge, fewer patients developed a palpable seroma in the experimental group: 10 in the experimental group versus 28 in the control group ($P = 0.001$). Fewer seromas needed aspiration (mean 1 [range 0–3] in the experimental group vs. mean 4 [range 1–5] in the control group; $P < 0.001$). There were no significant differences in terms of the incidence of complications associated with axillary lymphadenectomy ($P = 0.941$).

Conclusions. OK-432 is a feasible and safe option for axillary lymphadenectomy for breast cancer. The use of it does not always prevent seroma formation, but it can reduce drainage magnitude and duration, as well as decrease the incidence of seroma after the removal of drainage. It may be increasingly conducted in day surgery clinics.

Axillary lymphadenectomy remains an integral part of treatment for breast cancer for lymph node positive patients. A significant incidence (15–81 %) of complications is still associated with axillary lymphadenectomy, including lymphorrhea, lymphoceles, seroma formation, and in rare cases lymphedema (swelling of the arm).[1–5] Some patients can avoid axillary dissection as a result of the technique of sentinel lymph node biopsy; however, there is still a large percentage of patients who have to undergo axillary dissection, especially for those who have positive axillary lymph nodes.

Although seroma is not a serious complication, the occurrence of it may cause wound infection and dehiscence, delay recovery time, prolong the period of hospitalization, increase costs of treatment, and even delay the initiation of adjuvant therapy.[6–9] Therefore, it has been a major concern for both surgeons and patients. Many different methodologies have been used to reduce seroma formation and prevent

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axillary leakage after axillary lymphadenectomy for breast cancer, including external compression, a delayed program of arm exercises in the recovery phase, ultrasound cutting devices, suction drainage, fibrin glue, bovine thrombin, tetracycline, and talc poudrage.[6,10–22] Thus far, no practical guidelines exist to prevent the occurrence of seroma, the result of conflicting trial results.

OK-432 (Sapylin) is a lyophilized streptococcal preparation made from a low-virulence strain (Su) of *Streptococcus pyogenes* (group A) incubated with penicillin.[23] It has been successfully used as an immunotherapeutic agent in many types of malignancies.[24–27] Its immunopotentiating actions are caused by strong local inflammation that promotes the release of various cytokines such as interferon gamma, interleukin-1 and -2, or tumor necrosis factor.[28] It has also been widely accepted that OK-432 is effective in reducing ascites and pleural effusion in patients with carcinomatous peritonitis and pleuritis.[28] However, studies of the effectiveness of OK-432 in reduction of seroma formation after axillary lymphadenectomy for breast cancer have not yet been reported. The purpose of this study was to investigate the effectiveness of action of OK-432 therapy in patients requiring axillary lymphadenectomy.

PATIENTS AND METHODS

From July 2010 to November 2011, a total of 111 patients were assessed for eligibility. All patients had sentinel lymph node–positive breast cancer and required either a mastectomy or quadrantectomy plus axillary lymphadenectomy. The following patients were excluded from this study: (1) penicillin skin test positive; (2) known blood-clotting disorders; (3) currently receiving anticoagulant treatment; (4) diabetes mellitus or hyperpietic; (5) obesity (body mass index of >35 kg/m^2); (6) no previous surgery on the axillary lymphatic system; and (7) planned immediate reconstructive surgery. Patients who agreed to the study criteria were randomly divided into two groups, the experimental group and the control group. OK-432 applied to the axillary fossa plus placement of closed suction drainage was used in the experimental group; placement of closed suction drainage only was used in the control group. A prospective randomized study was designed to evaluate the efficacy of OK-432 to reduce seroma formation after axillary lymphadenectomy for breast cancer. Most of the surgeries in the study applying the use of OK-432 were performed by the same team of surgeons, which decreases possible bias.

Randomization was performed before the study (using numbered and sealed envelopes). Patients enrolled onto the study did not know their treatment group before the trial. We also did not inform them the possible outcomes of application of OK-432.

Approval was sought from Wenzhou Medical College Ethics Committee for Human Research before initiating the study, and informed consent was obtained from all patients.

Surgical Technique

In the operating theater, the patients in the study were positioned with their arms of the operated side adducted and flexed at 120°. In all 111 cases, axillary dissections involved all the three axillary lymph node levels. Lymph nodes and all tissue inferior to the axillary vein, between the anterior border of latissimus dorsi and the medial to the medial border of pectoralis minor up to the apex of the axilla, were excised en bloc. The long thoracic and thoracodorsal nerves were preserved. However, the intercostobrachial nerves were resected if necessary. During the surgical procedure, in order to control the homeostasis, we decided to use knot-tying ligations and bipolar electrocoagulating instead of any other device.

After completion of the axillary dissection, the wound was irrigated with physiological saline. Then, after randomization, a single suction drain was brought out below the incision before wound closure in the control group. In the meantime, patients in the experimental group continued to receive 100 mL of OK-432 mixture (10 kU OK-432 and saline) sprayed into the axillary wound. We also used the mixture to soak the wound for 30 min. At the end of the surgical procedures, patients were fitted with a suction drain at the axillary fossa, and the wound was closed by means of a continuous intradermal suture line. We removed the drains when the daily drainage volume was less than 80 mL. None of the patients in two groups underwent immediate reconstruction.

Primary Outcome

All 111 patients completed follow-up visits at the first week for ultrasound assessment of the amount of fluid present in the axilla. The presence of clinically palpable fluid collection was considered a palpable seroma and was treated by aspiration. A clinically palpable seroma was not considered a postoperative complication.

The primary outcomes of the study included the following: (1) mean total drainage volume; (2) postoperative day of drainage removal; (3) 1 week after drainage removal, number of patients who developed a palpable seroma; and (4) number of seroma aspirations of every patient needed at ultrasound assessment. The volume of drainage was measured by a surgeon who was not informed of each patient's treatment group and was not involved in the patient's operation. Ultrasound assessment was done by the same ultrasonologist, and fluid was suctioned out with an echo-guided evacuative puncture, if necessary.

Statistical Analyses

This was a prospective randomized clinical trial. Normally distributed continuous data were assessed by Student's *t* test. Categorical data were tested by standard χ^2 test with or without Yates's correction. Noncontinuous parametric variables were analyzed by the Mann-Whitney *U*-test. All statistical data were calculated with by SPSS statistical software, version 17.0 for Windows (SPSS, Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 111 consecutive patents were enrolled onto the study. There were 54 patients in the experimental group and 57 patients in the control group. Demographic characteristics of the patients are listed in Table 1. The clinical characteristics of 111 patients in the two groups did not represent significant variables in terms of seroma magnitude. It is worth noting that there was no significant relationship in either patient group between seroma formation and type of surgical procedure conducted (mastectomy or quadrantectomy). All 111 patients completed follow-up visits at the first week for ultrasound assessment of the presence of seroma.

A summary of outcome measures after surgery in patients treated with or without OK-432 is provided in Table 2. The mean total drainage volume was of 325.22 ± 67.23 mL in the experimental group and 362.07 ± 75.98 mL in the control group ($P = 0.008$). Compared with patients in the control group, patients in the OK-432 group had a significantly shorter duration of axillary drainage (4.52 ± 1.09 days vs. 5.16 ± 1.31 days; $P = 0.003$). One week after hospital discharge, ten patients developed a palpable seroma in the experimental group versus 28 patients in the control group ($P = 0.001$). We used ultrasound assessment for the presence of seroma to check the number of seroma aspirations of every patient, if necessary. Patients in the experimental group had significantly fewer evacuative punctures (mean 1 [range 0–3] vs. mean 4 [range 1–5], $P < 0.001$).

With regard to complications after surgery, there were no injuries of the thoracodorsal nerves or the long thoracic nerves in any patient in the two groups. The incidence of complications associated with lymphadenectomy was 7.4 % (one flap necrosis, two wound dehiscence, one surgical wound infection) and 5.3 % (one flap necrosis, one wound dehiscence, one surgical wound infection) in patients who underwent surgery with and without OK-432, respectively ($P = 0.941$).

TABLE 1 Patient characteristics

Patient characteristics	Experimental group ($n = 54$)	Control group ($n = 57$)	*P*
Age (years), mean ± SD	56.69 ± 9.79	57.72 ± 10.45	0.592
Body mass index (kg/m^2), mean ± SD	24.44 ± 2.05	23.88 ± 1.97	0.144
Treatment received			
Mastectomy	31	33	
Quadrantectomy	23	24	0.959
No. of removed lymph nodes, mean ± SD	16.81 ± 5.23	18.16 ± 4.32	0.142
Tumor size			
≤10 mm	7	5	
11–30 mm	32	36	
31–50 mm	11	13	
≥51 mm	4	3	0.655
Lymph node status			
N+	34	30	
N−	20	27	0.271

TABLE 2 Outcomes after surgery

Outcome	Experimental group	Control group	*P*
Mean total drainage volume (mL)	325.22 ± 67.23	362.07 ± 75.98	0.008
Mean duration of axillary drainage (d)	4.52 ± 1.09	5.16 ± 1.31	0.003
No. of patients who developed a palpable seroma	10	28	0.001
No. of seroma aspirations at ultrasound assessment, mean (range)	1 (0–3)	4 (1–5)	<0.001
No. of complications	4	3	0.941

DISCUSSION

Although the application of sentinel lymph node biopsy is widely accepted as a standard procedure because of its high sensitivity and accuracy in predicting axillary lymph node status, there are still a number of situations where a conventional axillary lymphadenectomy is indicated, especially for those patients with positive or suspect axillary lymph nodes based on an objective examination and an instrumental diagnosis. In these patients, there are still complications after axillary lymphadenectomy, in particular seroma formation.[1–5] It is crucial to note that although fewer axillary node dissections may be performed, there is still a sizable percentage of patients who will get seromas after sentinel node biopsy. Lucci et al. found that there is a

6 % seroma rate after sentinel lymph node dissection, and efforts to reduce seroma are still clinically important, especially in obese patients.[29] Even though seroma is not a serious complication, it accounts for significant patient expense and morbidity, including delayed discharge, healing, and in some cases even delay in supplementary radiotherapy and chemotherapy treatments.

The formation of seroma can be the result of several factors—for instance, small vessel injury in the axillary or the creation of dead space caused by the removal of tissue and inflammatory reaction.[5,30] Bonnema et al. analyzed chemical and cellular composition of axillary drainage fluid after axillary lymphadenectomy and found that there was insufficient fibrinogen present in the seroma, which may give rise to seroma formation.[31] Hence, by utilizing these factors, an efficient method to reduce seroma formation may be found.

There are several methods for reducing seroma magnitude that are described in many published articles. Burak et al. reported that thrombin has no effect on prevention of seroma formation or decrease in the amount of wound drainage after axillary dissection, which may be because thrombin's hemostatic properties are inadequate and may be because of a lack of fibrinogen.[6] O'Hea et al. suggested that routine use of a compression dressing is not warranted, and that it could even increase the incidence of seroma formation after drain removal.[11] Shamley et al. in a systematic review and from evidence from randomized controlled trials, noted that the use of a delayed program of arm exercises may reduce seroma formation, but firm conclusions could not be drawn because of clinical and statistical inconsistencies between studies.[12] Galatius et al. affirmed the effect of an ultrasonic energy dissection technique.[13] Rice et al. reported a nonsignificant difference in the incidence and degree of seroma between patients with or without topical tetracycline because of rich lymphatic supply as well as extensive lymphoid tissue and subcutaneous dissection.[21] Some of these techniques show a decrease in seroma formation; however, there are some complications associated with the respective methods, and the views of surgeons vary for some techniques, such as the efficacy of fibrin glue, and the use or not of drainage.[4,8,17,19,32–36] Therefore, up till now, a definitive and safe method for decreasing incidence of seromas in breast cancer surgery has not yet been recognized.

OK-432 has been widely applied in patients with malignant effusions.[37] Recently, OK-432 has also been used in benign lesions such as lymphatic malformations, with good treatment results.[38,39] OK-432 may induce an inflammatory response at the site of spray, leading to sclerosis and occlusion of the sites of lymphatic leakage. However, the role of OK-432 in the treatment of reducing seroma formation is unclear.

The results of our study showed that palpable seroma formation occurred significantly less often when OK-432 was used during surgery. Fewer seromas needed aspiration in the experimental group than that in the control group. Furthermore, the use of OK-432 yielded a slight advantage in reducing the mean duration and total volume of drainage. One week after hospital discharge, ultrasound assessment for the presence of seroma found fewer in patients treated with OK-432, thus further emphasizing the efficacy of OK-432. We removed drains when less than 80 mL in 24 h drained instead of less than 30 mL, which is performed in Europe and the United States; therefore, the seroma rate was much higher than we see in the United States. However, the application of OK-432 decreased the amount of fluid visible on ultrasound and shortened the time to drain removal; these are important end points that are clinically important for patients, who can then prepare for further treatment. No statistically significant difference between the groups of patients was found regarding the incidence of complications after axillary lymphadenectomy, indicating that OK-432 is a safe and effective option.

In conclusion, seroma formation is regarded as more of a nuisance than a true complication after axillary dissection. The results of this study indicate that OK-432 is a feasible and safe option for axillary lymphadenectomy for breast cancer. Compared with the conventional approach without OK-432, it has the advantages of reducing drainage magnitude and duration, and decreasing the incidence of seroma. OK-432 provides a good option for the reduction or prevention of seroma formation after axillary lymphadenectomy.

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