ORIGINAL ARTICLE

ROLE OF OCTREOTIDE IN CONTROL OF LYMPHORRHEA AFTER AXILLARY NODE DISSECTION IN MASTECTOMY OPERATIONS - A RANDOMIZED CONTROLLED STUDY

By
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Aim: *Lymphorrhea and seroma formation are disabling and serious complications of axillary lymphadenectomy. The role of octreotide in control of post axillary dissection lymphorrhea will be assessed in this study.*
Methods: *Fifty female patients with cancer breast of different stages were subjected for modified radical mastectomy and divided into two groups; the first group was given octreotide (Sandostatin, Novartis Pharma AG, Basle, Switzerland) 0.1 mg subcutaneous / 8 hours for 7 days, the other group was the control group. Both groups were evaluated for amount and duration of lymphorrhea as well as infection and hematoma formation.*
Results: *A significant difference in the amount and duration of lymphorrhea between the two groups was observed (P = 0.0003). In the first 8 days, the mean amount of lymphorrhea was 145.0 ± 45.8 cc per day and mean duration of drainage was 27.0 ± 7.59 days in control group. In the treatment group, the mean amount of lymphorrhea was 104.0 ± 29 cc per day and the mean duration of drainage was 12.7 ± 6.74 days.*
Conclusion: *Octreotide could be used successfully for control of post-axillary lymphadenectomy lymphorrhea and this may lower the incidence of lymphedema and lymphosarcoma.*
Keywords: *Somatostatin, post mastectomy seroma, axillary lymphadenectomy.*

INTRODUCTION

Breast cancer remains the most common cancer diagnosed in women, approximately one third of all breast cancers are hormone-dependent.[1] Axillary lymph node dissection for staging and local control of nodal disease is an integral part of breast cancer therapy.[2] After axillary dissection, seroma formation is the most common early complication with a reported incidence of 5% to 80%.[3,4] The etiology of seroma formation is multifactorial and includes the use of electrocautery, surgically created dead space, local inflammation and lymphorrhea from severed lymphatic vessels. Seromas are thought to self propagate by inducing inflammatory mediators.[5-7] A number of measures have been attempted for prophylaxis and treatment of seroma formation, these include placement of drains, sclerotherapy, pressure dressing, repeated aspiration, avoiding electrocautery, fibrin sealant and careful ligation of lymphatic vessels. These measures have not been uniformly adopted because of their own complications and high failure rate.[5-8]

Somatostatin is a tetradecapeptide hormone with many physiological and pharmacological action. It can inhibit gastrointestinal endocrine and exocrine secretions and motility as well as hepatic and splanchnic blood flow. In animal models, systemic somatostatin reduced local inflammation which is an important mechanism in seroma formation. Direct effect of somatostatin on lymphatic flow has been observed in the gastrointestinal tract only.[9-11] Octreotide, a long acting synthetic analogue of somatostatin with 20 times the potency of its natural peptide, has been used in the treatment of chylous ascites and thoracic duct injury by reducing lymphatic production

from gastrointestinal tract.[12] The precise mechanisms responsible for this action are not well studied but the inhibitory action of somatostatin on splanchnic blood flow and triglyceride absorption is believed to be at least partially responsible.[9] Somatostatin receptors have been found in lymphatic tissues within and outside the gastrointestinal tract.[11,12] It is likely that somatostatin can exert a direct effect on the lymphatic system to reduce lymph production.[2]

This study aims at assessing the effect of postoperative octreotide administration on amount and duration of drainage and local complications from the surgically created dead space after mastectomy and axillary lymphadenectomy in patients with breast cancer.

PATIENTS AND METHODS

This study was conducted at General Surgery Dep., Mansoura University Hospital from March 2003 to May 2005. Fifty female patients were included in the study. They were having cancer breast of different stages for whom modified radical mastectomy (MRM) was indicated. Patients who had had surgery to their axilla before or who were undergoing simultaneous breast reconstruction were excluded from the study. None of the studied patients were diabetic. Routine laboratory investigations and metastatic work up was done for all cases. After informed consent, MRM was done with axillary dissection extending to level II lymph nodes. Diathermy dissection and electrocautery was used in all cases. Tube drain on 0 suction of 22F was inserted in all cases and secretions were recorded. The patients received third generation cephalosporins for 5 days. Local sealants (fibrin glue) and pressure bandages were not applied. The patients were divided randomly into two groups;

- The first group (treatment group) (30 patients). They received octreotide (Sandostatin, Novartis Pharma AG, Basle, Switzerland) 0.1 mg subcutaneous / 8 hours for 7 days, starting from the first post-operative day
- The second group (20 patients) was the control group and received no treatment.

Postoperative surveillance protocol included clinical evaluation for daily drainage, development of seroma (fluctuant swelling in the surgically created dead space with no local signs of inflammation), hematoma formation (soft swelling, non fluctuant with bluish discoloration of overlying skin), and infectious complications (local inflammatory signs with purulent discharge). The clinicians responsible for follow up were blinded about the nature of treatment the patients received.

Side effects of octreotide were recorded (expected side effects included local irritation, hypersensitivity skin reaction, bradycardia, anorexia, nausea, vomiting, abdominal pain and distension and pain in injection site). The drains were removed when the amount of daily drainage became 50 cc or less and the patients discharged after recording time of drain removal and duration of drainage. After discharge, all patients were seen three times a week for the first six weeks, weekly for the first three months and monthly after that. Repeated aspiration was done for patients with seromas and the amounts were calculated.

The resected specimens were examined for number of lymph nodes removed and number of positive lymph nodes.

Statistical methods: The Findings assessed were calculated as numbers, simple percentages and mean ± standard deviation. Statistical analysis was done using Chi-square test and student t test.

RESULTS

Demographic characteristics and laboratory investigations of the studied patients (age, weight, height, Hb and albumin) showed no significant difference between both groups. Mean body mass index (BMI) was 30.3 ± 1.6 in treatment & 26.1 ± 1.8 in control group Table 1.

Pathological examination revealed no difference in staging between treatment and control group (P = 0.93) (Fig. 1). Postoperative complications included hematoma formation (one case in each group) and wound infection which was higher in control group (one patient in treatment and two patients in control group) (3.3% vs10%).

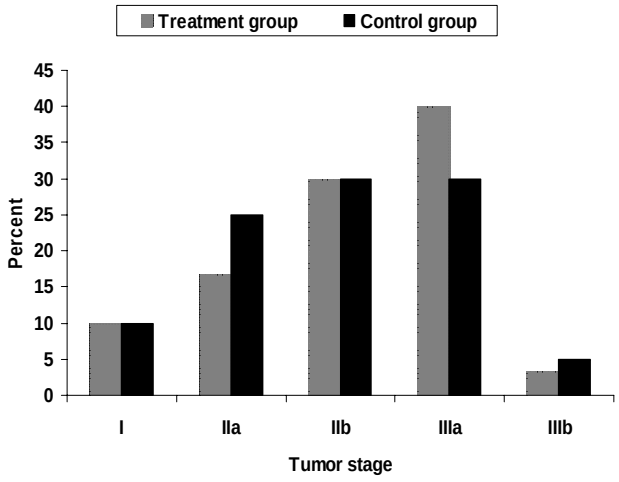

Fig 1. Tumor Staging in the Studied Groups.

There was no significant difference in the range and mean number of excised lymph nodes (LN) between both groups (P = 0.14). LN infiltration was significantly higher in treatment than control group (P = 0.044) Table 2. On calculating total amount of drainage in the first 8 days, there was a highly significant difference in the mean amount of drainage between both groups (the amount was much higher in control group) (P= 0.0003) Table 2.

The mean amount of daily discharge in the first 8 days was significantly higher in control group after the first postoperative day (P = 0.0004) (Fig. 2). By eighth day, the drained fluid became less than 50 cc in 66.7% of patients under treatment while it was more than 50 cc in 95% of control group (P = 0.0001) Table 2.

After removal of drains, seroma collected in 40% of treatment group patients and in 90% of control group (P = 0.0001) Table 2. Duration of drainage and aspiration ranged from 5 to 28 days with mean duration of 12.7 ± 6.7 days in treatment group while drainage and aspiration ranged from 8 to 42 days with mean period of 25 ± 9.57 days in control group (P = 0.001) Table 2. The side effects of octreotide reported in the study were minimal and included local irritation at injection site and nonspecific gastrointestinal discomfort.

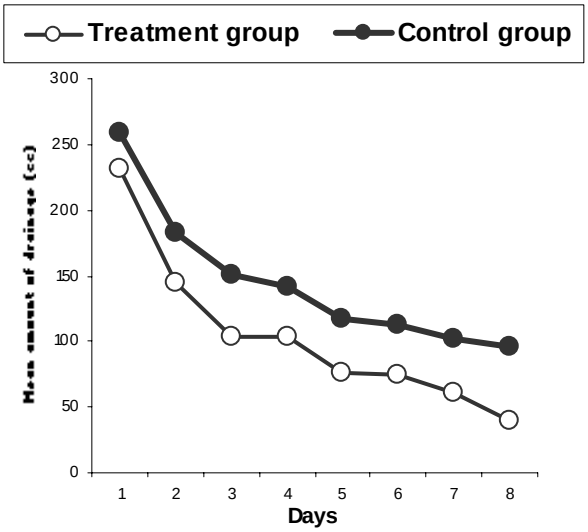

Fig 2. Mean amount of drainage in 1st 8 days in the studied groups.

Table 1. Demographic Characteristics of the Studied Groups.

	Treatment Group (n=30) Mean ± SD	Control Group (n=20) Mean ± SD	(P) Value*
Age	46.7 ± 8.68	49.4 ± 9.69	0.31
Weight (Kg)	78.8 ± 9.25	73.4 ± 10.2	0.059
Height (cm)	163.0 ± 8.45	167.0 ± 6.35	0.090
BMI	30.3 ± 1.6	26.1 ± 1.8	0.072
Hb (gm%)	11.4 ± 1.08	11.4 ± 1.10	0.99
Albumin(gm%)	3.8 ± 0.466	3.71 ± 0.38	0.47

* Student t test

Table 2. Clinical results of the Studied Groups.

		Treatment Group (n=30)	Control Group (n=20)	(P) Value
Excised LN:	Mean ± SD	12.6 ± 4.27	14.4 ± 4.1	0.14 (t)
Infiltrated LN:	Mean ± SD	7.75 ± 5.57	4.80 ± 4.50	0.044* (t)
Drainage / day in the first 8 days:				0.0003*
	Mean ± SD	104.0 ± 29.0	145.0 ± 45.8	(t)
Removal of drains:	≤ 8 days (n)	20 (66.7%)	1 (5%)	0.0001*
	> 8 days (n)	10 (33.3%)	19 (95%)	(X2)
Aspiration after drain removal:				
	Aspirated (n)	12 (40%)	18 (90%)	0.0001*
	Not aspirated (n)	18 (60%)	2 (10%)	(X2)
Duration of drainage	Mean ± SD	12.7 ± 6.74	25.0 ± 9.57	0.0001* (t)

t = Student t test X2 = Chi-square test.
* Significant values.

DISCUSSION

Seroma formation after axillary lymphadenectomy in women with breast cancer remains a problem despite many effort to reduce surgery-related morbidity.[5-8,13] Seroma may lead to infection; prolong hospital stay and delay chemotherapy and radiotherapy.[14]

Patient's mean age was compatible in both groups. The published data showed higher mean age[2] but other demographic features as weight, height and BMI were not mentioned. Mean BMI was insignificantly higher in treatment than in control group (P = 0.072).

In a literature, a correlation between the BMI and the exposed surgical area was statistically significant (P < 0.002), as well as the day the drains were extracted (P < 0.05).[15] Seroma formation is suspected to be more in patients with higher BMI. The reverse occurred in our study where treatment group with higher BMI and larger surgically created dead space give less seromas and shorter period of drainage.

Postoperative infection rate was less in treatment (3.3%) than control (10%) group. These complications were higher than that reported in literature.[2] The lower incidence of infection in treatment group may be referred to use of octreotide which affected seroma formation. Patients having the lowest volumes of edema fluid have the best chance for successful outcome with minimum morbidity.[16] On inducing chemical burn in an animal, use of octreotide markedly reduced the amount of dermal seromas and subsequently incidence of infection.[17] Infectious complications delay adjuvant therapy and cause lymphatic obstruction and lymphedema. Use of octreotide from this point of view is supported strongly by the results.

In contrary to a published study,[2] there was insignificant difference in mean number of excised LN between both groups (P = 0.14). This difference is explained by the extensive axillary dissection which extended to level III LN.[2] The role of axillary dissection as an effective means of controlling regional nodal disease has long been recognized but its therapeutic impact has been questioned as axillary dissection is associated with significant complications including cutting and destruction of lymphatic vessels.[18] Assuming that more nodes extracted might cause more cutting of lymphatic vessels resulting in more lymph leak and subsequently seroma formation. These facts strengthen our hypothesis of using octreotide after nodal dissection especially with extensive axillary dissection.

LN infiltration was significantly higher in treatment group (P = 0.044) in accordance with a similar study (P = 0.025) (2). The mean number of infiltrated LN was much higher in our study. LN infiltration leads to more lymph vessel obstruction raising incidence of lymphedema. As octreotide could reduce lymph production,[11] lymphedema is suspected to be less with treatment.

The mean amount of collected fluid per day in the first 8 days was significantly higher in control group (P = 0.0003). Our results are the same as in a literature.[2]

The mean amount of lymphorrhea in each day of the first 8 days showed a significant difference after the first postoperative day (P ranged from 0.033 in the second day to 0.0001 in eighth day) which indicates the therapeutic effect of octreotide. This effect may be attributed to its direct effect on lymphatic system reducing lymph production,[11] or its anti-inflammatory action. Since inflammatory responses play an important role in seroma formation, this might be an important mechanism by which octreotide reduces lymphatic drainage after axillary dissection. In an experimental study, octreotide protected against sepsis-induced oxidative tissue injury.[19]

By the 8th day, the drains were removed from 66.7% of patients in treatment group which is a highly significant difference from control group (P = 0.0001). In a published study, the difference in the mean period of drain removal was insignificant (P = 0.30).[2] Repeated aspiration was done for patients showing seromas which were detected in 40% of patients under treatment and in 90% of control group. This means that after drain removal, treatment group gave good response in spite of discontinuation of treatment. This result may help in reducing the dose and duration of treatment and consequently the cost (about 600-700 Egyptian Pounds per course). So, in the future the cost will be less as the course of treatment will be shorter and will be tailored according to patient's response as regard amount and duration of drainage.

The total period of drainage was much lower in treatment group (P = 0.0001) which is more than that published[2] but with the same significance values. This difference may be due to different demographic characteristics.

The significant decrease in amount and duration of drainage in our study and in published data in association with negligible side effects and less infection rate, favor the use octreotide to control lymphorrhea as this will improve patient's quality of life, decrease surgery related morbidity, shorten hospital stay and give the chance for early adjuvant treatment to be started.

Our results suggests that other risk factors as anthropometric features, method of dissection, type of drains, serving lymphatic vessels and use of local sealants should be taken into consideration together with octreotide. Also, the development of oral octreotide preparation with higher activity, stability, bioavailability and longer duration of action might be beneficial especially for home therapy.[20]

In conclusion; Octreotide can be used successfully for control of post-axillary lymphadenectomy lymphorrhea. Further study with longer follow up is required to determine the optimal dose, timing, duration of treatment and, more important, its role in prevention of lymphedema and lymphosarcoma. Potentially, octreotide may be used in similar situations of regional lymph node dissection.

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