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RESEARCH ARTICLE

IMPORTANCE OF NUTRITION IN THE DEVELOPMENT OF SEROMA AFTER BREAST SURGERY

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ABSTRACT

Purpose: To investigate the importance of nutrition in the development of seroma after breast surgery. Seroma is the most common complication after mastectomy where the incidence varies between 10 and 50%. Seroma is a complication which may lead to delayed additional treatment due to skin necrosis, infection, delayed wound healing, and should be taken seriously.
Material and Methods: Totally 40 rats, divided into groups of 10, were used in this experimental study. Group 1 (control) was fed normal rat feed, Group 2 was fed normal rat feed at a rate about 70% of that of Group 1 (malnutrition), and Group 3 and 4 was fed protein-rich diet (Glutamine-Arginine-Methyl Butyrate) (10g protein /kg/day) for 7 days preoperatively, and unilateral (right) pectoral major muscle excision and axillary dissection were performed in the groups and on Day 7. Postoperatively, Group 1 was fed normal rat feed, Group 2 was fed normal rat feed at a rate about 70% of that of the control group, Group 3 was fed normal rat feed and Group 4 was fed protein-rich diet for 10 days. On postoperative day 10, seroma samples were collected and the animals were sacrificed.
Results: Seroma volumes were 1.5ml (1ml-2.5ml) in the control group, 1.5ml (1ml-2.75ml) in the malnutrition group, 1ml (0.5ml-1ml) in Group 3 (fed protein-rich diet preoperatively), and 0.75ml (0.5ml-1ml) in Group 4 (fed protein-rich diet preoperatively and postoperatively). The seroma volumes were expressed as median values. Based on these values, the seroma volumes were significantly lower in the groups which were fed protein-rich diet (p=0.001).
Conclusion: According to results of recent study, we can advocate that, administration of protein-rich diet both pre- and post-operatively may lead to reduction in seroma formation. We believe that clinical studies should be planned in a similar manner.

Keywords: seroma, nutrition, breast surgery, experimental rat model, protein rich diet

INTRODUCTION

Today, although modified radical mastectomy (MRM) is still valid, breast conserving surgery (BCS) methods are preferred in suitable cases. However, complications can be seen in any of the the surgical interventions applied on breast. These complications are wound infection, hematoma, seroma, nerve injury and lymphedema, which are commonly seen after mastectomy and axillary dissection (AD) (1). Among those complications, seroma is the most common one occurring after breast cancer surgery with an incidence of between 10% and 50% (2-5). Seroma can also develop after any surgery performed by elevation of skin flaps. It occurs as a result of leakage of lymphatic and vascular fluids into the dead space created by tissue removal in tissue dissection (2,4).

Seroma is considered more acceptable by many surgeons than the other serious complications since it recesses with aspirations that usually take several weeks (5). However, seroma can lead to serious complications such as wound infection, lymphedema, flap necrosis, prolonged hospitalization, sepsis and delayed initiation of adjuvant therapy (3, 5). In a study that compared the seroma contents with lymph and plasma, it was seen that seroma contains high molecular weight proteins such as protein, albumin, globulin and LDH at significantly higher rates (2). Seroma is the entire fluid collection led by lymphovascular leakage and exudate resulting from prolonged inflammatory process (4). The present study investigated the effect of nutrition on seroma. It was thought that administration of protein-rich diet would increase the blood albumin and prealbumin levels, accelerate the wound healing process, and reduce the seroma volume via these mechanisms. Studies were conducted using Fibrin Glue, Tetracycline HCL, Talk, 5 Fluorouracil substances and Corynebacterium Parvum bacterium to prevent seroma, however the results were unsuccessful. (6-8). Recent research is the first study which investigate the relationship between seroma and nutrition in literature.

MATERIAL AND METHODS

The study was conducted at the Adnan Menderes University Veterinary Faculty Experimental Animal Laboratory between February and March 2013, after obtaining the approval of the University's Local Animal Ethics Committee (B.30.2.ADÜ.0.00.00.00/050.04/2012/100, Date: 13.10.2012). 40 female Wistar-Albino rats were used. The rats, weighing averagely 310 grams. We divided the rats into 4 groups and each group included 10 rats. Group 1 was fed normal rat feed for 7 days preoperatively and for 10 days postoperatively. Group 2 was fed normal rat feed at a rate about 70% of that of the control group (malnutrition) for 7 days preoperatively and for 10 days postoperatively. Group 3 was fed protein-rich diets for 7 days preoperatively and normal rat diet for 10 days postoperatively. Group 4 was fed protein-rich diet for 7 days preoperatively and for 10 days postoperatively.

Surgical Procedure

The rats were weighed before being anesthetized. The rats were administered a mixture of 30 mg/kg ketamine hydrochloride (Ketalar, Pfizer, P.I, Turkey) and 8 mg/kg xylazine (Xylazine Bio, Bioveta, P.I, Turkey) via intraperitoneal injection.

Five minutes after the anesthesia; abdominal skin was cleaned with povidone-iodine (Figure 1). After a midline incision from the sternal notch to xiphoid, a skin/subcutaneous flap was detached from the thoracic wall and the major pectoral muscle was dissected from the thoracic wall. At this stage, the brachial plexus, brachial vein and axillary artery were observed and preserved (Figure 2). Preserving these formations, the fatty cellular tissue and lymph nodules in the axillary fossa were dissected and excised. Then the major pectoral muscle was excised by ligating with 4/0 silk sutures at the location it was attached. The skin was primarily closed using 4/0 silk sutures.

Group I - Control group (K)

Group II - Malnutrition group (M)

Group III - The group fed protein-rich diet preoperatively (P)

Group IV - The group fed protein-rich diet preoperatively and postoperatively (PP)

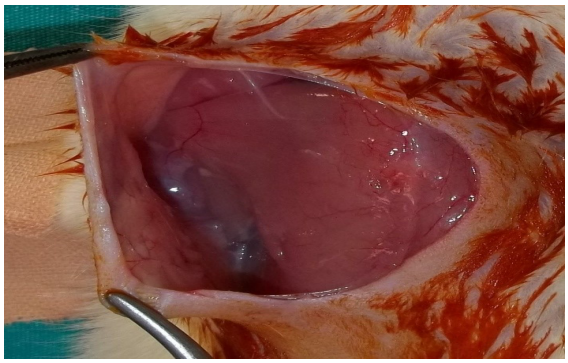

Figure 1. Appearance of pectoral muscle after the flap dissection

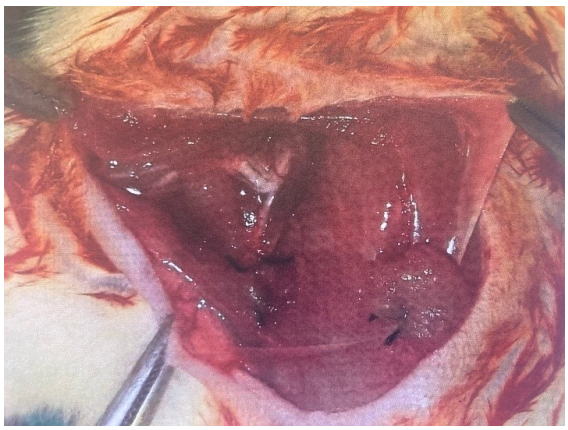

Figure 2. The pectoralis major muscle excised, axillary dissection completed. The brachial plexus, thoracodorsal nerve and axillary vein are seen.

Table 1. Mean seroma volumes in the groups

	K	M	P	PP	p
Seroma (ml)	1.5 (1.0-2.5)	1.5 (1.0-2.75)	1.0 (0.5-1.0)	0.75 (0.5-1.0)	0.001

Control group (K), Malnutrition group (M), Group fed with diet rich in preoperative protein (P), Group fed with diet rich in preoperative + postoperative protein (PP) milliliter (ml)

Table 2. Mean VEGF, IL-1 and albumin values in the groups

	K	M	P	PP	p
VEGF (pg/ml)	380.14 (353.89-399.60)	330.32 (298.00-374.78)	346.57 (305.67-363.89)	369.25 (328.26-414.51)	0.183
IL-1 (pg/ml)	874.66 (776.33-889.00)	890.66 (868.16-893.08)	836.66 (710.33-894.16)	721.00 (486.91-886.83)	0.194
Albumin (g/dl)	2.70 (2.65-2.80)	2.55 (2.40-2.67)	2.80 (2.7-2.85)	2.85 (2.70-2.92)	0.003

Control group (K), Malnutrition group (M), Group fed with diet rich in preoperative protein (P), Group fed with diet rich in preoperative + postoperative protein (PP) milliliter (ml)

The seroma fluids were analyzed for inflammation parameters, i.e.IL-1ß (acute phase reactant) and VEGF (the key parameter of vessel proliferation and angiogenesis). IL-1β and VEGF levels were determined using rat ELISA kit.

In the tissue samples taken, fibrin, bleeding, edema, vascular congestion and PMNL were semi-quantitatively determined as acute inflammation parameters. Fibrous tissue increase, fibroblasts, lymphocytes and macrophages were evaluated as chronic inflammation-wound healing parameters. PMNLs were evaluated in terms of wound activity. Vascular congestion, proliferation and density parameters were evaluated.

Cellular and histopathological scoring was semi quantitatively determined using 5 categories. According to this, cellular density was evaluated as (-): none, (+): minimal (<10%), (++): 20-30%, (+++): 50%, (++++): > 50%.

Statistical Analysis

Conformity of the quantitative data to normal distribution was analyzed with the Kolmogorov-Smirnov test. As the quantitative data did not conform to normal distribution, analyses were performed in the groups using Kruskal Wallis test and multiple comparisons of the groups were made. The descriptive statistics were expressed as median values (25-75th percentile). The qualitative data were analyzed using Fisher's exact chi-square test and the descriptive statistics were expressed as frequencies (percent). $p<0.05$ was considered statistically significant.

RESULTS

Macroscopic Results

Seroma volumes were 1.5ml (1ml-2.5ml) in Group 1, 1.5ml (1ml-2.75ml) in Group 2, 1ml (0.5ml-1ml) in Group 3 (fed protein-rich diet preoperatively), and 0.75ml (0.5ml-1ml) in Group 4 (fed protein-rich diet preoperatively and postoperatively). (Table 1) The seroma volumes were expressed as median values. Based on these values, the seroma volumes were significantly lower in the groups which were fed protein-rich diet (p=0.001)

Biochemical Results

Vascular Endoshelial Growth Factor (VEGF): No statistically significant differences were found in VEGF levels between the groups (p=0.183). (Table 2)

Interleukin 1(IL-1): No statistically significant differences were found in IL-1 levels between the groups (p=0.194). (Table 2).

Albumin: Statistically significant differences were found in albumin levels between group II(M) and group II (P) (p=0.031), and between group II (M) and group IV(PP)(p=0.002). Blood albumin levels were higher in the groups fed protein-rich diet than in the malnutrition group(p=0.003). (Table 2).

Histopathological Results

Statistically significant differences were found among the groups in terms of vascular proliferation rate (p=0.003; Fisher's exact test), edema rate (p=0.006; Fisher's exact test), congestion rate (p<0.001; Fisher's exact test), fibroblast rate (p=0.003; Fisher's exact test), lymphocyte rate (p<0.001; Fisher's exact

test), macrophage rate (p<0.001; Fisher's exact test). These parameters were the lowest in group IV.
No statistically significant differences were found among the groups in terms of fibrin rate (p=0.059; Fisher's exact test), bleeding rate (p=0.178; Fisher's exact test), polymorphonuclear leukocyte (PMN) rate (p=0.063; Fisher's exact test), fibrous tissue increase rate (p=0.083; Fisher's exact test).

DISCUSSION

Studies to date could not clearly describe the pathophysiology of seroma. Seroma is the fluid accumulation led by lymphatic and vascular leakage into the dead space created by tissue dissection or tissue removal. Seroma can also develop after any surgery performed by elevation of skin flaps (9,10). The pathogenesis of seroma could not be clearly understood. It is considered as a inflammatory exudate formed in response to surgical trauma and the acute phase of would healing. Oertli et al. claimed that fibrinolytic activity contributes to seroma formation (11).
When the results of the studies conducted to date are reviewed, another randomized controlled study by Vaxman et al. suggested that fibrin glue increases seroma formation (12).
In a progressive randomized study by Petrek et al., the numbers and sizes of the axillarl lymph node formation were mentioned as the most affecting factor for seroma formation (13). Mobilizing shoulder earlier after surgery increased seroma formation in the studies conducted by Schultz, Abe and Shambley while causing no change in the studies conducted by Petrek, Jansen and Zavotsky (13).
Gonzales et al. and Hashemi et al. suggested that the most important factor affecting the incidence of seroma is the surgical technique (14,15).
In a randomized study by Rice et al., no effect of local tetracycline on the seroma formation after mastectomy was found (16).
Compressive dressing increased seroma formation in the study conducted by O'Hea et al., while causing no significant change in the study by Say et al. (17,18).
In a study conducted by Parikh et al., withdrawal of drains on postoperative day 3 and day 6 did not cause any difference in seroma formation (19).
In a study conducted by Purushotham et al., using no drain after using this technique did not increase seroma formation (20). Coveney et al. demonstrated that this technique reduces seroma formation (21). In another study by Ağalar et al, it is depicted that in order to reduce postop seroma, different biological materials are used. (22)
Large dissection in MRM causes blood and lymphatic vessel damage which results in blood and lymphatic leakage thereby causing seroma formation (23). As a result of inflammation, supply of blood, which predominantly contains phagocytes, to the area changes the concentration of soluble particles in the area. When the particle concentration within seroma is higher than the surrounding area, an osmotic differential pressure is generated. This results in fluid supply to the area until the particle concentrations are equalized (14,15). Histamine, prostaglandin and adenosine are responsible for inflammation and vasodilation. While macrophages and leukocytes with polymorph cellular nuclei migrate to the area with these cellular mediators, the vascular terminuses, which had been closed with vasoconstriction, open and contribute to fluid flow.
This fluid has been described as a fluid consistent with exudate which contains cellular components of acute inflammation (23). Although many ways were tried, no way to prevent seroma could be found.
Recent studies demonstrated that seroma is different from lymphatic fluid, rather having a nature of "inflammatory exudate".
It has been considered as a prolonged inflammatory response or a prolonged initial phase of wound healing (1,4). This indicates that seroma forms due to some deficiencies in wound healing.
The importance of nutrition in would healing is a fact which is known since the era of Hippocrates. In malnourished patients, incomplete and delayed wound healing are observed and such patients are under the risk of developing wound infection because of insufficient defense mechanism against infections. In experimental animals, when normal nutrition is restricted by 60%, impairment in collagen cruciate ligaments was seen within 1 week and reduction in collagen synthesis was seen within 4 months (24). Protein deficiency (malnutrition or Kwashiorkor) plays a key role in delayed wound healing (25). Moreover, all aspects of wound healing impair in such cases. Normal protein synthesis and cell proliferation cannot occur without appropriate amino acids. In fact, in experimental animals with no protein intake fibroplasia, matrix formation, angiogenesis and wound sampling show defects (26-28). Protein deficiency also impairs the host's cellular and

humoral immune systems. In addition, edema developed due to hypoalbuminemia causes blockades around normal wounds.

In our study, the groups fed protein-rich diet, the groups fed normal feed and the malnourished groups were compared with respect to postoperatively formed seroma volumes.

The median seroma volumes were 1.5ml (1ml-2.5ml) in the control group, 1.5ml (1ml-2.75ml) in the malnutrition group, 1ml (0.5ml-1ml) in Group 3 (fed protein-rich diet preoperatively), and 0.75ml (0.5ml-1ml) in Group 4 (fed protein-rich diet preoperatively and postoperatively). Based on these values, the seroma volumes were significantly lower in the groups which were fed protein-rich diet (p=0.001).

In the groups fed protein-rich diet preoperatively and both pre- and postoperatively; blood albumin levels were higher than the malnutrition group.

CONCLUSION

Histopathologically; statistically significant differences were found among the groups in terms of vascular proliferation, edema, fibroblast, lymphocyte and macrophage rates. In the group groups fed protein-rich diet both pre- and postoperatively, vascular proliferation, edema, fibroblast, lymphocyte and macrophage rates were lower than the other groups. Statistically significant difference was found among the groups in terms of congestion rate. In the groups fed protein-rich diet, congestion date was lower than the other groups.

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Conflict of interests: None.
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