ORIGINAL ARTICLE

EFFECTS OF LOCAL ANTI-INFLAMMATORY DRUGS ON SEROMA FORMATION AFTER MASTECTOMY AND AXILLARY LYMPH NODE DISSECTION IN THE RAT MODEL

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ABSTRACT

Purpose: The aim of this study was to examine the protective effects of nonsteroid anti-inflammatory drugs (NSAIDs) and steroids on seroma formation after mastectomy and axillary lymph node dissection in rats.

Methods: Mastectomy and axillary lymph node dissection were applied to the rats. Thirty rats enrolled in the study were randomly divided into three groups of 10 each. Group I patients received physiological serum, whereas groups II and III received 30 mgr/kg methylprednisolone sodium succinate and 0.2 mgr/kg meloxicam, respectively. All groups received the local drug applications into the potential space beneath axillary and pectoral flap before skin and subcutaneous tissue were closed. After 7th day of mastectomy, the seroma volumes were measured in groups and the rats were sacrificed.

Results: The seroma amount showed significant increase ($p<0.05$) in group 1 when compared to group 2 and 3. However no significant differences were observed between group 2 and group 3. The postoperative infection rate was 40 percent in group 2.

Conclusion: It was concluded that methylprednisolone sodium succinate and meloxicam were effective on the seroma formed after radical mastectomy and axillary dissection. However, due to the high risk of wound infection of methyl prednisolone sodium succinate, this should not been preferred.

Keywords: Anti-Inflammatory agents, mastectomy, rat, seroma, steroid

INTRODUCTION

Seroma is a conjoint complication of mastectomy and axillary dissection. The incidence of this seroma complication varies between 3-85%[1,2]. Procedures having high incidence for seroma are surgical operations such as abdominoplasty, rhytidectomy, face-lifting, latissimus dorsi flap and serratus anterior excision[3]. Seroma can cause ischemia, necrosis, infection or wound dehiscence in pectoral and axillary flap. These complications and especially seromas reduce quality of life in patients[4,5].

Many surgical and medical approaches have been developed for seroma treatment[1,3,6,7]. Axillary drainage amount can be decreased by some methods such as suturing skin flaps to pectoralis major muscle, suturing dead-gaps, making aspiration drainage, delaying-limiting shoulder movements, using fibrin glues[8].In recent years, there are some popular clinical and experimental studies[3,9-12] which include synthetic glutaraldehyde-based tissue adhesive, phenytoin, 5-fluorouracil, fibrin glue usage. Rat model of mastectomy and lymph node dissection has been shown to provide ideal environment for postoperative liquid accumulation. Many various agents have been suggested in different studies[13-15] for decreasing seroma amount after mastectomy and axillary dissection. In literature, there is no sufficient information about effect of local NSAID (non-steroid anti-inflammatory drug) and steroids on seroma formation. COX-2 inhibitors and steroids decrease prostaglandin and leucotriene synthesis via inhibiting cyclo-oxygenase-2 and phospholipase A2 enzymes. NSAID and steroids are supposed to decrease inflammation and liquid (seroma) formation. This study determined the possible effects of NSAID and local steroid on seroma formation after mastectomy and axillary lymph node dissection in rat models.

METHODS

Animals: The rat model of mastectomy and axillary dissection was performed on 30 Wistar albino rats

weighing between 200-250 gr. The animals were housed under standard laboratory conditions. Standard food pellets and tap water were available ad libitum.

Surgical Technique: The experimental protocol was approved by the Ethical Committee. The animals were anesthetized with5 mg/kg of xylazine hydrochloride (Alfazyne®, 20 mg/ml, Alfasan, Woerden, Holland) and50 mg/kg of ketamine hydrochloride (Alfamine®,100mg/ml,Alfasan, Woerden, Holland). The anesthetic agents were administered intramuscularly. After laying the rats in supine position, left upper and both lower extremities were fixed. Left upper extremity was tractioned upwards and laterally. Mid-sternal skin incision was performed starting from jugular fossa to xiphoid process in rats according to the method defined Harada et al.[11]. Skin and subcutaneous flap were dissected from thorax wall on left side. Pectoralis major muscle was dissected and excised starting from sternum to insertion point at caput humeri. Lymph nodes in the axillary fossa were dissected under pectoralis minor muscles. Major vascular structures were protected during dissection. In order to increase seroma formation, lymphatics and blood vessels were traumatized 35 times with scalpel (no:15) under the pectoral flap in the subcutaneous tissue on the dorsal surface of the flap. Haemostasis was performed in excised and axillary regions. Potential gap was dried with sponges. All the rats were randomly allocated to one of the three groups (n = 10 each). Group I received physiological serum; group II received 30 mgr/kg methylprednisolone sodium succinate (Prednol-L®, 250 mg/ml, Mustafa Nevzat, İstanbul, Turkey); and group III received 0.2 mgr/kg meloxicam (Melox®, 15mg/1.5 ml, Nobel, İstanbul, Turkey).All groups received the local drug applications into the potential space beneath axillary and pectoral flap. Skin and subcutaneous tissue were closed and wound surface was cleaned with povidone iodin, after this cleaning, wire mesh was fixed over the wound surface via 3-0 prolen sutures to avoid rats to bite the incision line.

At postoperative 7th day, subject rats were given anesthesia again. Seroma was aspirated with insulin syringes from traumatized surfaces. Then, sutures were removed and rest of all seroma was aspirated. After aspiration of all seromas, subject rats were sacrificed.

Statistical Analysis: All groups were statistically compared according to seroma amounts with Kruskal-Wallis test, and the groups were compared two-by-two with Mann Whitney U test. $P < 0.05$ was considered statistically significant.

RESULTS

Group 1 (physiological saline solution, control group) average aspirated seroma amount was 1.35 ml, standard deviation was 0.31 ml (minimum 0.7 ml to maximum 1.8 ml) and median value was 1.35 ml.

Group 2 (Methylprednisolone sodium succinate, steroid group) average aspirated seroma amount was 0.15 ml, standard deviation was 0.14 ml, minimum value was 0 ml, maximum value was 0.5 ml and median value was 0.1 ml. Wound infection was seen in four of 10 rats (40%) in this group.

Group 3 (Meloxicam, NSAID group) average aspirated seroma amount was 0.23 ml, standard deviation was 0.21 ml, minimum value was 0.1 ml, maximum value was 0.7 ml and median value was 0.1 ml.

Figure shows aspirated serum levels in three groups. When we compared group 1 versus group 2, we found that group 2 had significantly lower seroma amount than group 1 ($p< 0.05$). Similarly, when we compared group 1 versus group 3, we found that group 3 had significantly lower seroma amount than group 1 ($p< 0.05$). When we compared group 2 versus 3,no significant difference was observed between groups ($p> 0.05$). However, rats in group 2 had infection (4 of 10, 40%) on wound area on 7th day. Infection was at the dehiscened (opened) incision lines. Thus, steroid group drugs have potential to precipitate wound area infection; we have to report this significant finding as well.

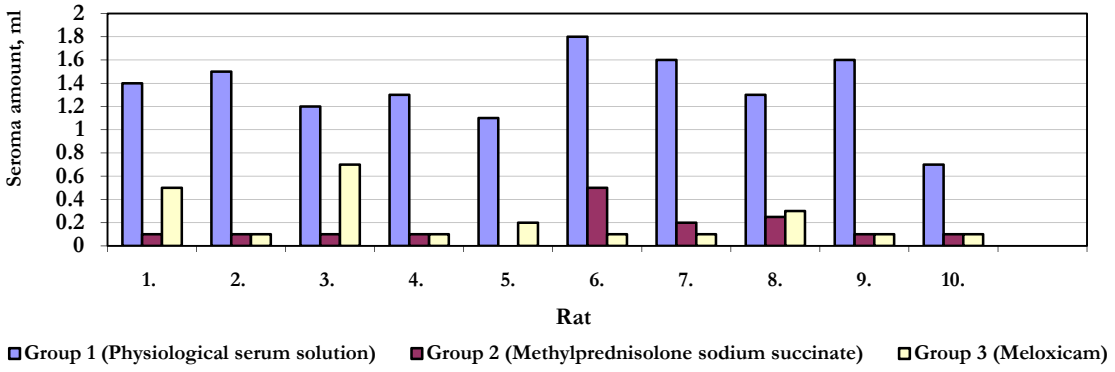

Figure 1: Aspirated seroma levels at the end of postoperative 7th day (ml).

DISCUSSION

In the present study, we described for the first time the impacts of NSAID and local steroid drugs applied locally on the seroma formed after mastectomy. There are many alternative treatment protocols for early stage

breast cancer. Although conservative surgery has been more preferred recently, there were no significant decreases considering the seroma incidence[3]. Inflammatory processes take place leading to accumulation (of macrophages, polymorphonuclear leukocyte etc.) in potential gaps. This accumulation was shown pathophysiologically after surgery[16].

Inflammatory processes lead to secretion of mediators such as histamine, prostaglandins, adenosine etc. These mediators were shown both at tissue level and in blood. So that, these mediators increase permeability and cause serious drainage. Serous collection and seroma occurs[16,17].

After axillary dissection, the most important risk factors for seroma formation are extent of surgically traumatized area, increased surface area, old age, increased body mass index, increased body weight, anemia and other factors[6,18]. Many experimental studies were conducted in order to decrease seroma amount after mastectomy. Chilson et al. reported that seroma volumes and incidence decreased from 38.6 to 25% which were taken out of thorax wall together with multi-layered sutures[19].This is still a high incidence; 25% will have seroma which is a very high incidence. Porter et al. observed seroma in 38% patients on whom electrocoterization was used; however they observed seroma in 13% patients with use of scalpel in their retrospective study[20]. In a prospective randomized study of Lumachi et al., seroma occurred in 20% of patients when they preferred ultrasonic dissector. However, they reported 40% seroma incidence with use of scalpel during mastectomy[1]. Manouras et al. preferred electro thermal bipolar vessel sealing system in their surgeries and they reported seroma levels very low[21].

Today, one of the methods in order to prevent and eliminate seromais closed negative pressure drainage system[18]. However, this application may lead to bacterial invasion and deep wound infection, because pathogenic agents may migrate in retrograde way[22]. Suction drains with high (60-250 mmHg) absorption power may cause widespread flap necrosis and peripheral nerve injury[23].

When seroma occurs after removing the drainage systems, sclerosant agents may be preferred. These methods are controversial because repetitive aspirations may disturb and discomfort patient. Tetracycline was used as sclerosant agent. Tetracycline HCL may cause excruciating pains[24,25]. Foreign object reactions and allergic reactions were reported on patients with talk (powder) use[25,26]. Throckmorton et al. used ethylene glycol and povidon iodine as sclerosant agents but they reported that infection developed in 44% patients in long-term[27]. Erythromycin is another sclerosant agent to prevent seroma formation[28]. The effect of fibrin-glue was also reported in decreasing postoperative seroma drainage; both duration and amount[12].However, fibrin-glue is an expensive product and this is its biggest disadvantage. Corynbacterium parvum (Cp) is a strong sclerosant agent in addition to its non-spesific immune-stimulant-anti-tumoral activity. However, Cp has several side effects such as fever, nausea, vomit, tachycardia, leukocytosis andsplenomegaly[29]. Kocdor et al reported that locally applied 5 FU decreased seroma after mastectomy with its anti-inflammatory feature in their animal study[9]. Hidar et al. compared ketoprofen (NSAID) versus placebo in terms of their effect on postoperative drainage duration and mass volume after breast surgery. Single dose200 mg ketoprofen (versus placebo) did not decrease postoperative drainage mass significantly. However, they also found that there was a significant difference between drainage in the first two days postoperatively[15].

Seroma occurs in the acute phase of inflammation. Seroma formation is an inflammatory response; there are studies reporting that application of pre-operative steroidal or non-steroidal anti-inflammatory drugs may prevent seroma formation[16].Taghizadeh et al. showed in a study of autologous latissumus dorsi breast reconstruction surgery that seroma rates decreased after administration of 80 mg Triamcinolone within cavity. The researchers did not find any increase in infection rates[30].

There is no study about possible effects of NSAIDs or local steroids on seromas after mastectomy. Glucocorticoids inhibit prostonaid synthesis when given as exogenous drugs. They interfere with prostanoid synthesis where arachidonic acid is synthesized from membrane phospholipids. Phospholipase A2 enzyme is inhibited at this stage and thereby synthesis of arachidonic acid decreases. So, synthesis of all prostanoids will decrease; namely prostaglandins, prostacyclins, tromboxanes, leucotrienes and their metabolites. At the same time, glucocorticoids provide anti-inflammatory actions via inhibiting production and secretion of cytokines such as IL-1, IL-6, TNF-alpha[13]. NSAID produce analgesic, anti-inflammatory and anti-pyretic effects. Aspirin and such kind of classical non-steroidal antiinflamatuary drugs only decrease prostaglandin and tromboxane synthesis. They do not affect synthesis of leucotriens. They produce their effects by inhibiting the cyclo-oxygenase enzyme. NSAIDs act by inhibition of pro-inflammatory prostaglandin production. As a result of inflammation, leucocytes are activated and concommitant events take place (integrin and selectine up-regulation and adhesion to vessel wall, margination etc). In addition, it is very important that NSAIDs decrease active oxygene radicals, they inactivate radicals and stabilize lizozomal membranes in inflammatory cells[14]. NSAIDs show their effects inhibiting cyclo-oxygenase which is the speed-limiting enzyme for prostanoid type molecules that play an important role in inflammation. Also, selective COX-2 inhibitors (coxibs) have same analgesic, anti-pretic and anti-inflammatory effects but they do not have any effect on COX-1.So, they have minimal gastric side effects. The reason why steroids have more potent anti-inflammatory effects is that they rely on their effect on decreasing leucotriens and other lipoxygenase products[7]. Steroids and NSAID inhibit inflammatory processes and inhibit seroma formation[15]. As they are cheap, accessible with lesser side effects compared to other drugs, we concluded that steroids

and NSAID may be used locally.

In our experimental study it's considered that local steroids and NSAIDs decrease seroma amount significantly. Hospitalization durations and costs would decrease in accordance. However, our limitation is wound-area-infection which was more frequent with steroid use. This is a marked disadvantage. We concluded that COX-2 inhibitor NSAID drugs appear to be more practical and beneficial in decreasing seroma formation. Further advanced clinical and experimental studies are needed in order to confirm these results and detect the effects of oral NSAID use.

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