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Research Article

Examination of the Effects of Celecoxib on Postmastectomy Seroma and Wound Healing

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Abstract

Objectives: To examine the effect of celecoxib on wound healing and development of seroma after mastectomy.

Seroma is an accumulation of serous fluid in dead space emerging after breast cancer surgery. The pathophysiology of seroma has not been clearly elucidated. Development of seroma leads to prolongation of hospital stay, increase in costs, ischemia of the flaps, infections due to fluid accumulation, and delayed adjuvant treatment.

Seroma is still a current problem, and the most common treatment method for this problem is drainage and repeated aspirations for 5–7 days after surgery.

Methods: The effect of celecoxib whose anti-inflammatory, antiangiogenic, and antioxidant effectiveness has been demonstrated in a mastectomy model applied on female Wistar rats has been investigated in the present study. A total of 20 rats including 10 rats in the control and 10 in the celecoxib group were studied.

Intraperitoneal 0.25 cc/250 g (20 mg/kg/day) celecoxib was administered to the celecoxib group for 5 days after mastectomy, and the same volume of physiological saline solution was given to the control group for 5 days. Rats were followed up for 10 days after surgery. During this process, vitality of the rats, movements of the extremities, wound healing conditions, wound infections, flap necrosis, and occurrence of seroma were recorded. At the end of this period, seromas were aspirated, tissue samples were retrieved, and the rats were sacrificed. Fibrin, hemorrhage, edema, vascularization, congestion, polymorphonuclear leukocytes, and increase in fibrotic tissue fibroblasts, lymphocytes, and macrophages were evaluated in tissue samples.

In seroma fluids, interleukin-1 beta (IL-1β), an acute phase reactant, and vascular endothelial growth factor, a vital parameter of vascular proliferation and angiogenesis, were examined.

Results: At the end of the experiments, the seroma volume decreased significantly in the celecoxib group (p=0.804; 0.001), the IL-1β level decreased significantly as detected in the biochemical examination (p=0.014), and in the histopathological examination, an increase in congestion in the celecoxib group was determined.

Conclusion: In conclusion, celecoxib markedly decreased interleukin and the volume of seroma after mastectomy; suppressed the level of an acute phase reactant, IL-1β; and demonstrated this effect through its anti-inflammatory activity. We believe that the effects of celecoxib should be investigated using different dose applications and larger number of subjects.

Keywords: Celecoxib; inflammation; mastectomy; seroma; wound healing.

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Seroma is the most common postsurgical complication in the treatment of breast cancer surgery.[1, 2] Its incidence varies between 10% and 52%.[3] Though it often regresses within a few weeks, it can persist for a few months in some patients.[1-4] It has been reported that it becomes apparent more frequently after modified radical mastectomy and axillary lymph node dissection,[2, 5] followed by sentinel lymph node biopsy,[6] breast-sparing surgery,[7] subcutaneous mastectomy, and nipple-sparing surgery.[8]

Wound healing is classically divided into three stages: inflammation, proliferation, and remodeling (Fig. 1). [2, 9] Nearly 1 hour after short-term vasoconstriction immediately following injury, activation of intrinsic coagulation chain, hemostasis, and clot formation reactions, the endothelial cyclooxygenase-2 (COX-2) enzyme is activated to synthetize prostaglandins that induce platelet disaggregation and vasodilatation and also synthetize leukotrienes to increase vascular permeability, chemotaxis, and leukocyte adhesion (inflammation) (Fig. 2).[9] Mastectomy is an ideal model for evaluating postsurgical acute inflammatory response and wound healing.[10] Extensive dissection during breast surgery leads to many blood and lymphatic vessel injuries, and subsequent blood and lymphatic leakage results in the formation of seromas.[11] It has been reported that this fluid is an exudate fluid containing cellular components of acute inflammation.[12] McCaul et al.[3] reported that the accumulated fluid after breast cancer surgery is the result of the exudative inflammatory phase of wound healing.

In the study conducted by Watt-boolsen et al., seroma was accepted as an indicator of the first phase of wound healing. [1] In another study, intracerebral hemorrhage was induced in the rat brain, and combined treatment with memantine and celecoxib was attempted. The authors indicated that when compared with memantine monotherapy, the combined therapy decreases functional losses, cerebral inflammation, and apoptosis, in addition to neuroprotective and anti-inflammatory activities of celecoxib.

It has been shown that celecoxib exerted this activity by increasing the level of prostaglandin E2 in the perihematomal area.[13] In the experimental arthritic mice model, celecoxib significantly inhibited joint pain and destruction (radiographic and histopathological evidence) with its anti-inflammatory effect.[14] In another experimental study, autoimmune encephalomyelitis was markedly suppressed by celecoxib, and it was stated that this agent may be a new treatment option in the treatment of multiple sclerosis.[15] Celecoxib has been shown to significantly reduce rat paw edema and amount of pleural exudate in air sac models induced with carrageenan.[16]

Celecoxib is a nonsteroidal anti-inflammatory agent used for its anti-inflammatory, analgesic, and antipyretic activities in human and various experimental animal models. Its mechanism of action depends on the inhibition of prostaglandin synthesis by the COX-2 enzyme.[17]

The aim of the present study was to investigate the efficacy

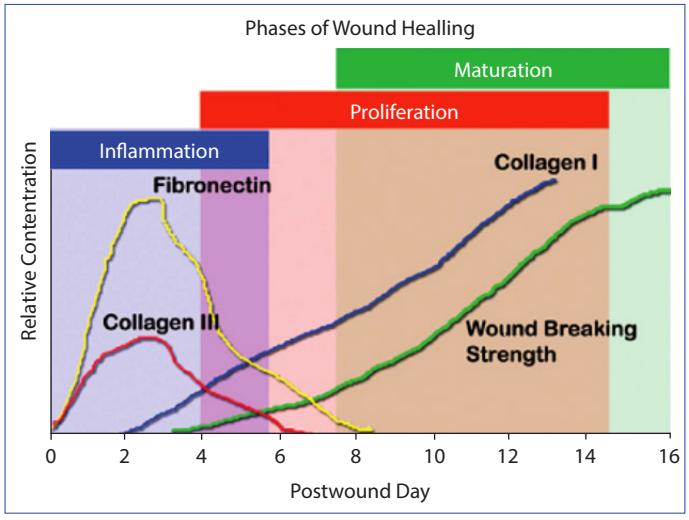

Figure 1. Schematization of wound healing phases (inflammation, proliferation, maturation) and concentration of wound matrix elements (collagen III, fibronectin, collagen I) in the wound area, and resistance to wound dehiscence during posttraumatic period [9].

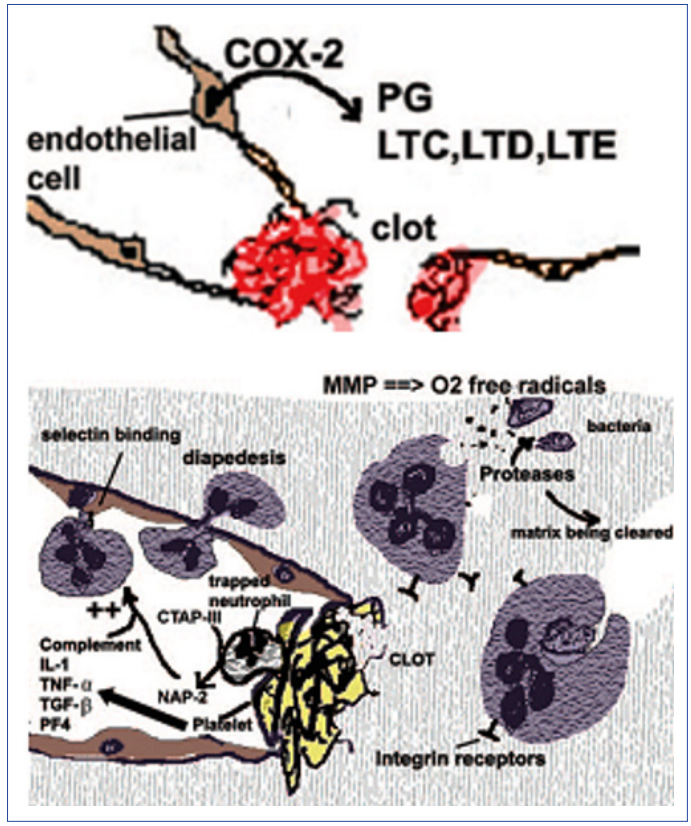

Figure 2. The role of cyclogenase -2 isoenzyme, and neutrophils in inflammation phase [9].

of celecoxib with its established anti-inflammatory, antiangiogenic, and antioxidant activities for seroma in a rat mastectomy model.

Methods

Experimental Animals and Groups

A total of 20 female Wistar rats with an average weight of 220.3 g were used in this experimental study. All rats were fed with standard laboratory chow and water. They were observed in an isolated environment under 12 h of alternate daytime and nighttime illumination and controlled ambient temperature (22±2 °C). Surgeries were performed in the animal laboratory under nonsterile clean conditions. Any prophylactic antibiotic was not administered preoperatively to prevent drug interaction. All rats were weighed preoperatively to estimate the dosages of drugs and amount of physiological saline (0.9% NaCl) to be administered.

Surgical Technique

All rats were treated with unilateral mastectomy and axillary dissection using the method described by Harada.[18] Intraperitoneal ketamine (50 mg/kg) and xylazine (5 mg/kg) anesthesia was administered, and the rats were fixed to the operating table with medicated plasters. The sternums of the rats were shaved with a razor blade and cleaned with 10% povidone–iodine solution (Fig. 3). After midline incision extending from the sternal notch to the xiphoid, the skin and subcutaneous flap were cleaved away from the thoracic wall (Fig. 4). The major pectoral muscle was dissected away from the thoracic wall. At this stage, the brachial plexus, brachial vein, and axillary artery were seen (Fig. 5). These anatomical formations were preserved, and the lymph nodes and adipose tissue in the axillary fossa were dissected and excised. Thereafter, the major pectoral muscle was excised with 4/0 silk sutures at the site where it was ligated. After hemostasis, physiological saline was administered to the control group, and celecoxib was given to the celecoxib group, and the skin flap was closed with continuous 4/0 prolene sutures (Fig. 6). Rats were divided into two groups:

Group 1 (control): In Group 1, 10 rats received daily intraperitoneal doses of 0.25 cc/250 g physiological saline for 5 days after their flaps were closed, and they were observed closely.

Group 2 (celecoxib): In Group 2, 10 rats received daily intraperitoneal doses of 0.25 cc/250 g (20 mg/kg) celecoxib for 5 days after their flaps were closed, and they were observed closely.

Rats were followed up for 10 days after surgery. During this process, vitality of the rats, extremity movements, wound healing conditions, wound infections, flap necrosis, and seroma (if any) were recorded. After administration of ketamine–xylazine anesthesia again on postoperative day 10, all seromas were aspirated with sterile syringes and quantified.

The previous incision was opened, and the seroma fluid remaining on the dissection side was aspirated again and added to the previous aspirates. These aspirates were collected in an Eppendorf tube for later examination in the biochemistry laboratory and stored at −70 °C. For histopathological examination, tissue samples were extracted from the skin, axilla, and chest wall on the dissection area and placed in a 10% formaldehyde solution. After all the procedures were completed, the rats were sacrificed using a high-dose ether anesthesia.

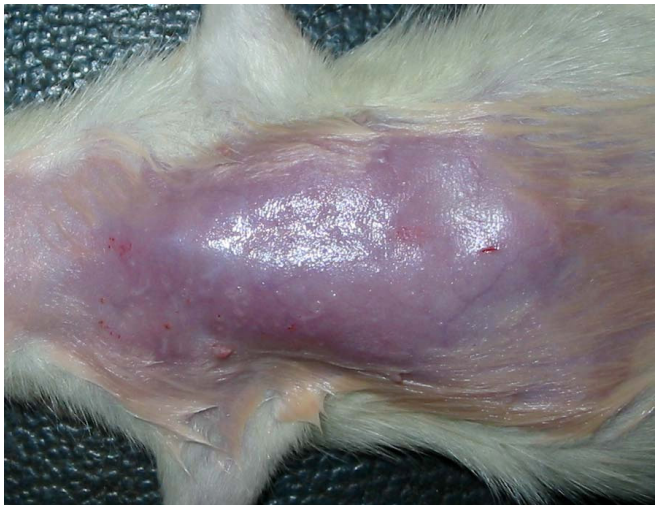

Figure 3. Preoperative appearance of the skin.

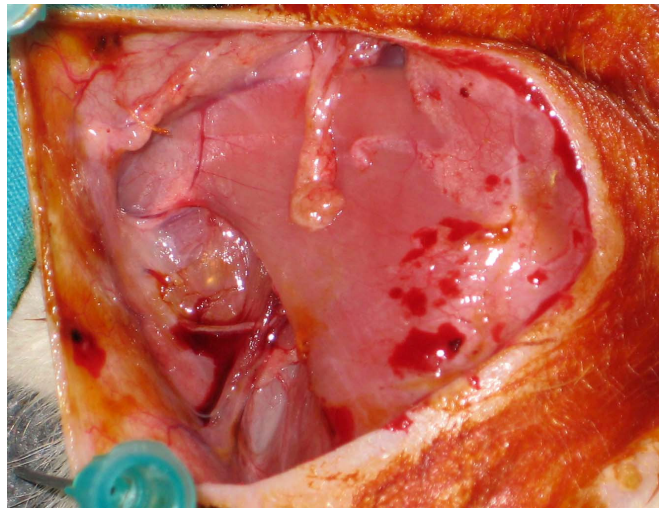

Figure 4. Appearance after dissection of the flap.

Analytical Procedures

Histopathological Examination Methods

Tissue samples obtained were sent for pathological examination in a 10% formaldehyde solution. All tissue samples were routinely processed. After embedding in paraffin blocks, 5-micrometer sections were made and stained with hematoxylin and eosin. Masson trichrome stain was applied to better evaluate the fibrous tissue. Thereafter, under a light microscope, necrosis, acute inflammatory granulation tissue, fibrous tissue, vascular characteristics, and microorganism population reflecting secondary infection were qualitatively assessed.

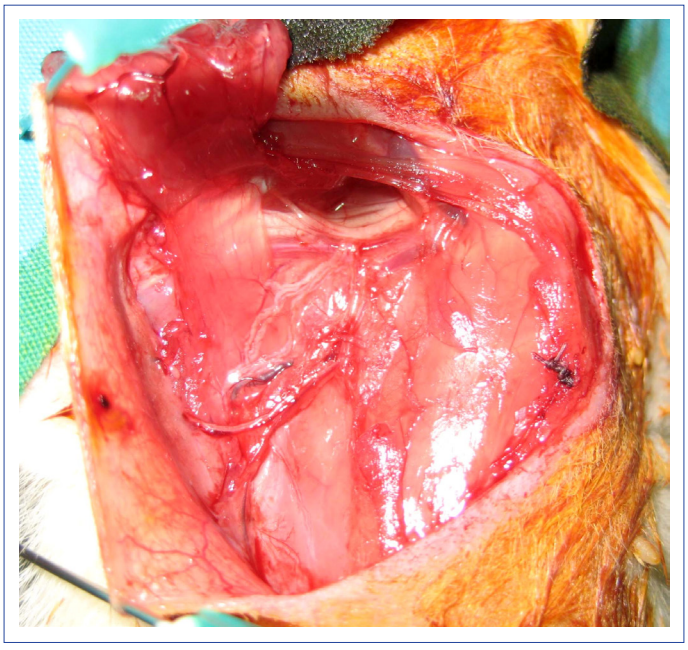

Figure 5. Intraoperative appearance: Major pectoral muscle was separated from the sternum, axillary dissection was completed, brachial plexus, thoracodorsal nerve, and axillary vein were exposed.

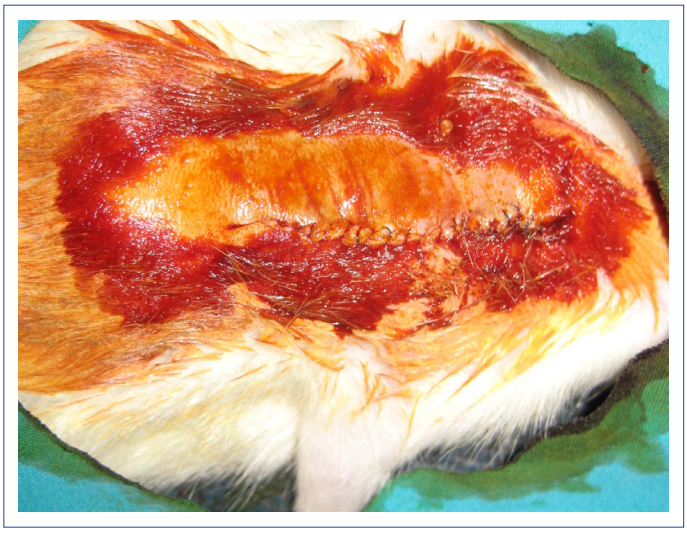

Figure 6. Surgical site appearance after closure of the skin flap.

As acute inflammation parameters, fibrin, hemorrhage, edema, vascularization, congestion, and polymorphonuclear leukocytes (PMNLs) were identified semi-quantitatively.

Increases in fibrotic tissue, fibroblast, lymphocytes, and macrophages were assessed as parameters of chronic inflammatory phase of wound healing. In terms of the activity of the wound, PMNLs were evaluated. Congestion, proliferation, and density parameters of the vessels were examined. For proliferation, numbers of the vessels and narrowness of their lumens, and for congestion, the lumens were checked for their spaciousness.

Cellular and histopathological scoring was evaluated semi-quantitatively at four stages. Accordingly, cellular density was as follows: 1 (–): absent, 2 (+): less, 3 (++): moderate, and 4 (+++): high (Table 1).

Biochemical Examination Methods

The collected seroma fluids were examined regarding interleukin-1 beta (IL-1β), an acute phase reactant of inflammation parameters, and vascular endothelial growth factor (VEGF), a basic parameter of vascular proliferation and angiogenesis.

The seroma fluid aspirated for biochemical examination was centrifuged at 4000 rpm to eliminate turbidity and particulate matter. The supernatants were stored at –70 °C and returned to room temperature until use. Then, the parameters of inflammation as IL-1β and VEGF that are acute phase reactants were analyzed using their specific kits and enzyme-linked immunosorbent assay method.

Statistical Methods

Statistical analysis was performed using the SPSS Data Editor for Windows version 15.0 program. Volumes of seromas and VEGF and IL-1β values were assessed using Mann–Whitney U test and histopathological parameters using chi-square test. Values of $p < 0.05$ or $\chi^2 < 0.05$ were considered significant.

Results

Each control and medication group comprised 10 rats. In the celecoxib group, wound infection and wound dehiscence were seen in one rat, whereas in the control group, a scarce number of microorganisms were seen in one rat; thus, these two rats were excluded from the study. Any evidence of infections was not found in other rats.

Macroscopic Findings

Infection: In the celecoxib group, infection and wound dehiscence were observed on day 6 after surgery, and

Table 1. Cellular and histopathological scoring of the celecoxib and the control (C) groups

Experimental rat no	C1	C2	C3	C4	C5	C6	C7	C8	C9	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10
Vascular proliferation	+	++	+	+	++	+	+	+	+	++	+	+	+	+	+	+	+	+	++
Fibrin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bleeding	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Edema	+	+	+	+	-	+	-	+	-	-	-	-	-	+	-	+	-	-	+
Necrosis	-	-	-	-	-	-	-	-	-	-	-	-	-	++	-	-	-	-	-
Congestion	++	+	++	+	+	-	-	+	-	-	-	++	-	-	-	++	-	-	-
Microorganism	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
PMNL	+	+++	++	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	++
Fibroblast	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	++
Lymphocyte	+	+	+	+	+	+	+	+	+	++	+	+	+	+	+	+	+	+	+
Macrophage	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Increase in fibrotic tissue	+	+	+	+++	+	+	++	+	+	+	+	+	++	+	+	+++	++	++	+

histopathologically, microorganisms were observed in one rat in the control group.

Restriction of movement of the forelegs: Within the first 3 days after the operation, restriction of movements of the forelegs was observed, and then they disappeared. However, in the celecoxib group in the rat that developed infection, difficulty in movements of the forelegs persisted up to postprocedural day 6. At that time, the rat was excluded from the experiment.

Macroscopic flap necrosis: Macroscopic flap necrosis was not seen in any of the subjects. As will be mentioned later, microscopic necrosis was detected in one rat in the control group.

Figure 7 shows the amounts of seroma fluids determined at the end of the experiments.

The mean amounts of seroma fluids in the control and celecoxib groups were found to be 1.19±0.074 ml (±SE) and 0.333±0.024 (±SE), respectively. Seroma volumes were found to be significantly lower in the celecoxib group (p≤0.001) (Figure 7).

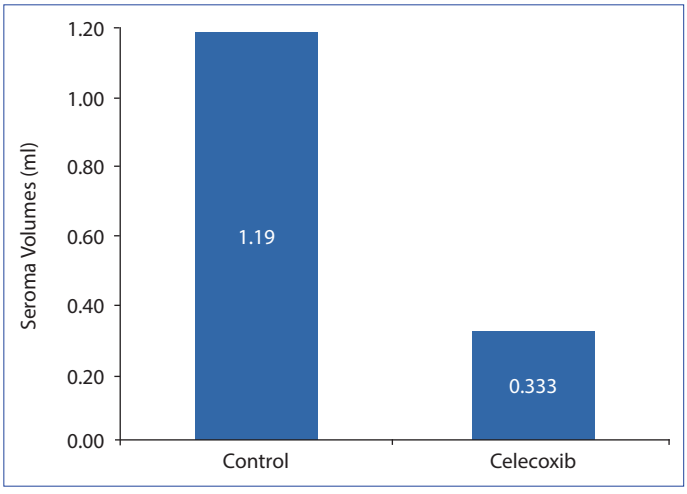

Figure 7. Volumes of seromas between experimental groups.

Histopathological Findings

Table 1 shows the cellular and histopathological scoring. C refers to rats given celecoxib, and K to the control group. Cellular density was as follows: 1 (–): absent, 2 (+): less, 3 (++): moderate, and 4 (+++): high (Table 1). There was no significant difference between the groups in terms of vascular proliferation, fibrin content, hemorrhage, edema, necrosis, microorganism populations, PMNL, fibroblasts, lymphocytes, macrophages, and fibrous tissue density.

Congestion: The congestion rate of the control group was significantly lower than that of the celecoxib group (p=0.044) (Figure 8).

Biochemical Findings

As biochemical parameters, VEGF and IL-1β were evaluated. C refers to celecoxib given to rats, and K to the control group (Table 2).

VEGF: There was no significant difference between the two groups in terms of VEGF levels (p=0.447).

IL-1β: A significant decrease was seen in the celecoxib group (p=0.014) (Figure 9).

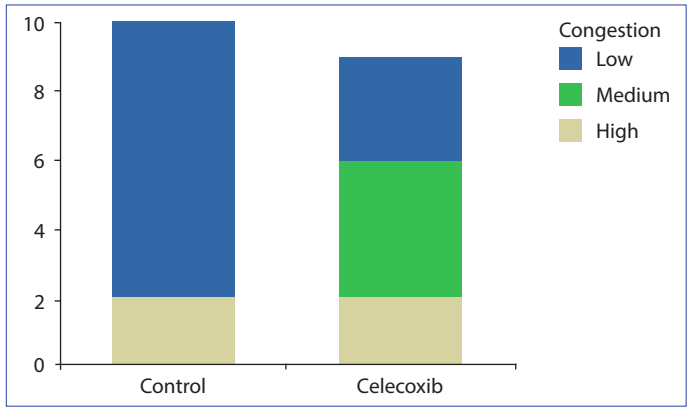

Figure 8. Distribution of congestion between groups.

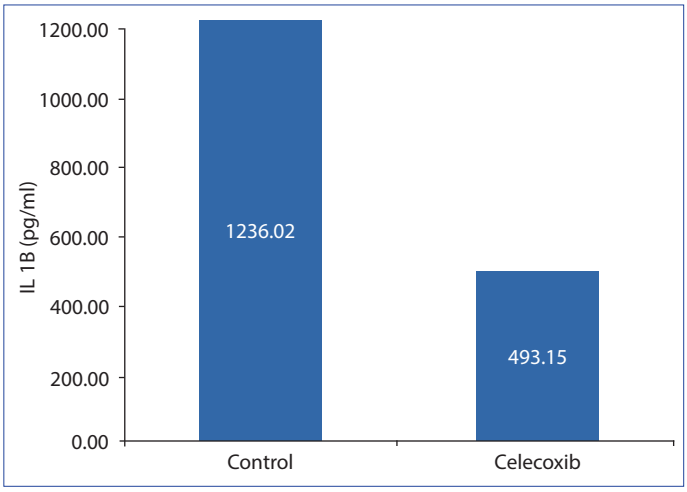

Figure 9. Comparison of IL-1ß levels between groups.

Discussion

The pathophysiology of seroma has not been clearly elucidated in previous studies.[2, 5] For the formation of seroma, weak adhesions of the flaps to the chest wall, perioperative dissection of the lymphatic and capillary vessels, wide dead space, pump effect of the arm and forearm muscles, local inflammatory mediators, and anatomical deformation of the axilla and chest wall have been held responsible.[3] Oertli et al.[19] showed that fibrinolytic activity contributes to seroma formation.

In an experimental study, Harada et al.[18] showed that they reduce the formation of seroma in mastectomized rats by using a fibrin glue. However, many randomized controlled trials have shown that fibrin glue or bovine thrombin does not have a marked effect in preventing seroma formation.[20-24] In another randomized controlled study by Vaxman et al., it was observed that conversely, fibrin glue increases seroma formation. However, Johnson et al.[25] have shown that the use of fibrin glue with or without drains does not have any advantage. In other studies of this series, it has been stated that preoperative and postoperative uses of fibrin glue and fibrinolysis inhibitors do not reduce seroma formation.[19, 20]

Several antineoplastics and many other methods and agents have been attempted in the prevention/inhibition of seroma including talc powder,[26] tranexamic acid,[19] *Corynebacterium parvum*,[27] tetracycline,[28, 29] polidocanol,[30] and octreotide[31] without any significant effectiveness of these alternatives, or they have not been used routinely due to their increased side effects.[32] It has also been observed that surgical fixation methods are ineffective in preventing seroma formation, leading to poor cosmetic results.

Significant efficacy of a more up to date tissue glue has not been found in the prevention of seroma formation. In their study of 215 patients, Eichler et al.[33] reported that in 205 patients, tissue glue shortens drain withdrawal time by 17% and prevents postoperative hematoma formation by 14%, but it does not cause any difference in seroma formation during follow-up of the patients.

Table 2. Rates of VEGF and IL-1β (pg/ml)

VEGF (K)	VEGF (C)	IL-1ß (K)	IL-1ß (C)
155.70	124.50	2457.21	494.73
137.40	141.00	1638.14	294.03
126.60	153.60	559.34	379.53
161.40	174.30	327.03	108.76
137.40	138.30	596.75	1172.85
146.10	141.90	571.80	337.97
150.60	135.30	1175.61	403.29
127.80	166.80	537.23	133.70
139.80	142.80	3328.68	1113.47
122.40		1168.48	

The frequently applied method in seroma treatment is drainage and repeated aspirations for 5–7 days postoperatively. The only significant outcome of the review study performed by Srivastava et al.[34] is that the patient who was discharged from the hospital could be managed by multiple aspirations of seroma.

The hypothesis concerning seroma formation that shows the accumulation of fluid with high osmotic pressure in the environment as a result of weak insertion of flaps on the chest wall and inadvertent cutting of the vascular and lymphatic vessels during dissection has not been fully clarified yet. It has been thought that the vasodilation due to the effect of inflammatory mediators migrating to the site of tissue trauma and the long-lasting leak that developed are involved in the etiology. Partially contradicting the thought that seroma is a classical simple exudate fluid according to molecular mechanism, the idea has arisen that advocates that seroma may be secondary to the prolonged inflammatory phase due to the disruption of some stages of wound healing.[1-3, 5, 35, 36]

It is evident that this phase may be shortened by COX-2 isoenzyme inhibition, and fluid accumulation may be reduced or prevented. Khan[37] stated that seroma could be reduced by anti-inflammatory effect. In our study, the hypothesis of the inhibition of COX-2 isoenzyme and the anti-inflammatory effect was targeted. However, with COX-2 enzyme inhibition, the entire wound healing process and wound resistance should not be impaired.

Müller-Decker et al.[38] have shown that in the wound healing model in rats, the inhibition of isolated COX-2 enzyme does not weaken angiogenesis and decrease collagen accumulation and wound resistance. In addition, in an experimental study by Blomme et al.,[39] it was seen that the inhibition of COX-2 isoenzyme does not prolong the wound

healing process. Based on these results and the outcomes of the aforementioned experimental models, the idea that it is possible to reduce the incidence of seroma by acting on the inflammatory phase without disrupting optimal wound healing has been reinforced.

In the present study, the efficacy of celecoxib whose anti-inflammatory and antiangiogenic activities in the rat mastectomy model have been shown was investigated in parallel with these considerations. In our study, owing to the development of infection and wound dehiscence, one rat in the celecoxib group, and owing to the detection of a small number of microorganisms during histopathological examination, two rats in the control group were excluded from the study. Since the histopathological examination of the remaining rats did not reveal the presence of any microorganism, it was considered that nonsterile but clean conditions were provided during the study.

In conclusion, in the celecoxib group, significantly decreased seroma volumes and lower levels of IL-1β in seroma fluid, which is one of the parameters of inflammation, are the results of the inhibition of COX-2 isoenzyme that suppressed the inflammatory phase of wound healing, further supporting the hypothesis of our study. However, as a result of the study, VEGF levels and vascular proliferation rates did not change between the two groups which made us think that celecoxib was not effective on the proliferation phase of wound healing that involves angiogenesis and lymphangiogenesis.

Significantly higher rates of congestion in histopathological examinations in the celecoxib group were conceivably related to the resolution of wound exudate by lipid mediators during the complex inflammatory phase and changes in time and extent of resolution due to the inhibition of prostaglandin. However, in support of these arguments, it is necessary to elucidate the complex wound healing process with many unknown aspects.

As a result of the biochemical data obtained from our study, it can be said that celecoxib systematically inhibits the formation of seroma through the suppression of acute inflammatory response rather than the inhibition of angiogenesis and/or lymphangiogenesis. As a result of histopathological data, systemic administration of celecoxib does not seem to have any effect at tissue level.

The current literature, on the other hand, maintains the popularity of the idea that the formation of seroma is due to an interruption in the wound healing process. Based on this, it would be appropriate to repeat this experimental study with different anti-inflammatory agents and different dosing schedules applied through different routes of administration in greater number of subjects.

Conclusion

Celecoxib, which is a COX-2 isoenzyme-selective anti-inflammatory agent administered at a dose of 0.25 cc/250 g (20 mg/kg/day) for 5 days, significantly reduced the incidence of postmastectomy seroma in rats. It significantly reduced IL-1β that is one of the inflammatory parameters in seroma fluids. It did not cause a significant change in histopathological parameters compared with the control group. The inflammatory phase of wound healing on the prevention of seroma formation should be further investigated in light of increased literature information.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – E.B.; Design – E.B., Ö.H.; Supervision – Ö.H.; Materials – E.B.; Data collection &/or processing – E.B.; Analysis and/or interpretation – E.B.; Literature search – E.B.; Writing – E.B.; Critical review – E.B., Ö.H.

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