Postmastectomy seroma: how much is it affected by serum levels of IL-6 and CRP and how much is it reduced by intravenous hydrocortisone injection?

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Background
Seroma is extremely common after breast surgery, and this could be because of the inflammatory response during wound healing. Several factors such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been detected in the seroma fluid that support this assumption; therefore, inhibition of the inflammatory response by using hydrocortisone might decrease seroma formation. We aimed to evaluate the effect of adding hydrocortisone to the anesthetic regimen in the perioperative serum level of IL-6 and CRP and consequently in postmastectomy seroma formation.

Patients and methods
The study included female patients with primary operable breast cancer who were randomly allocated to two groups; each included 40 patients. Patients in group I received general anesthesia with hydrocortisone, and patients in group II received general anesthesia without hydrocortisone. Venous samples were collected for measuring IL-6 serum levels before surgery, 6 h after the end of the procedure, and 24 h after the procedure and for measuring CRP serum levels before surgery and 24 h after the procedure. All patients were followed up postoperatively for registration of the total drainage volume until drain removal, timing of drain removal, incidence of seroma formation, and management of seroma.

Results
Patients in group I had a lower total drainage volume ($P = 0.001$), had the drain removed earlier ($P = 0.009$), and had a lower incidence of postmastectomy seroma formation ($P = 0.005$). Postoperative serum levels of IL-6 and CRP showed a significant decrease in group I compared with group II.

Conclusion
Postmastectomy seroma is likely a proinflammatory process and can be reduced by giving intravenous hydrocortisone on induction of anesthesia and 2 h later, which significantly decreases the inflammatory mediators (IL-6 and CRP) that significantly reduce the incidence of seroma.

Keywords:
C-reactive protein, hydrocortisone, interleukin-6, mastectomy, postmastectomy seroma

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Introduction

Breast cancer is the most common site-specific cancer in women; it accounts for 33% of all female cancers and is responsible for 20% of cancer-related death in women [1,2]. Seroma is extremely common after breast surgery, secondary to the rich lymphatic drainage of the breast and possibly the low fibrinogen levels and net fibrinolytic activity within lymphatic fluid collections [3]. Seroma, which is formed under the skin flaps of mastectomy wounds, impairs the healing process; that is why drains are usually left in place for 1–3 weeks, when the skin flaps heal and adhere to the chest wall, as evidenced by diminished drain output [4]. Seroma collections that develop after drain removal can be managed by percutaneous aspiration, which is usually well tolerated because the mastectomy and axillary incisions tend to be insensate; these procedures can be repeated as frequently as needed to ensure that the skin flaps are densely adherent to the chest wall; however, in rare cases when the seroma continues to recur, a Seroma-Cath may be considered [3,4]. Various methods, ranging from shoulder immobilization [5], perioperative use of tranexamic acid [6], prolonged suction drainage [7], and flap fixation [8,9], have been advocated with varying degrees of success in the prevention of seroma formation after mastectomy. Seroma formation is most likely the result of the inflammatory response due to wound healing; several factors have been detected in seroma fluid that support this assumption. These factors are high levels of IgG, leukocytes, granulocytes, proteinases, proteinase inhibitors, and different kinds of cytokines (tPA, uPA, uPAR, PAI-1, PAI-2, IL-6, IL-1) [10,11]. Moreover, interleukin-6 (IL-6) stimulates the liver secretion of C-reactive protein (CRP), which is now considered to be an

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important biomarker for proinflammatory status [12]. The use of hydrocortisone significantly decreased the inflammatory response in patients undergoing bilateral total knee replacement as measured by IL-6 production [10]. On the basis of this, an inhibition of the inflammatory response might result in a decrease in seroma formation, and perhaps improve the quality of life after mastectomy. Steroids inhibit the inflammatory response — for example, by inhibition of the cytokine function [10]. In this study, we aimed to evaluate the role of adding hydrocortisone to the anesthetic regimen in perioperative serum level of IL-6 and CRP and consequently in postmastectomy seroma formation.

Patients and methods

Patient selection

The study included female patients with primary operable breast cancer who were admitted to the hospital of the Medical Research Institute, University of Alexandria, Egypt, during the period from February 2013 to June 2014 and scheduled for a modified radical mastectomy. Patients with endocrine or metabolic disorders, diabetes, morbid obesity (BMI >40 kg/m^2 or 35 kg/m^2 with comorbidity), history of central nervous system diseases, who were under current or recent medication affecting the sympathetic response or hormonal secretion, such as carbamazepin, phenytoin, phenobarbital, rifampicin, salicylats, and ciclosporin, patients with distant metastasis, and patients who received previous anticancer treatment were excluded from the study. Institutional Research Committee approved the protocol before the study started. The study was explained to prospective patients and written informed consent was obtained before study entry.

Study protocol

All patients included in this study underwent complete history taking, full clinical examination, and laboratory and radiological investigations to exclude the presence of distant metastasis. Patients were randomly allocated to one of the two study groups; patients in group I received general anesthesia after insertion of an intravenous line, and standard monitors were attached. Preoxygenation was followed by induction with fentanyl 1 μg/kg, propofol 2 mg/kg, and cisatracurium 0.15 mg/kg. Two minutes later, an endotracheal tube was inserted and maintenance was ensured with isoflurane in oxygen. A dosage of 100 mg of hydrocortisone was administered at induction, followed by a second dose given 2 h later to patients in this group. Patients in group II received standard general anesthesia similarly to group I but without hydrocortisone and served as the control group. Venous samples were collected peripherally from an antecubital vein of the arm contralateral to the side of surgery using a small cannula.

For each patient, peripheral blood samples were collected for the following procedures: for measuring IL-6, the samples were collected at three time points — before surgery, 6 h after the end of the procedure, and 24 h after the procedure; for measuring CRP serum levels, samples were collected before the surgery and 24 h after the procedure. Serum and plasma samples were isolated from whole blood by centrifugation according to standard protocols. IL-6 was measured in serum samples by enzyme linked immunosorbent assay using an AviBion Human IL-6 ELISA Kit (Orgenium Laboratories, Helsinki, Finland) [13]. The CRP values were determined by turbidimetric immunoassay on an Olympus AU 400 autoanalyzer (Olympus, Hamburg, Germany) using Olympus Diagnostic reagents [14]. The detection interval for CRP was 0.08–160.0 mg/l, and the reference interval of serum CRP value was less than 1 mg/l [15] ghazals

Surgery was performed for all patients using the same technique irrespective of their randomization. The dissection of mastectomy flaps was performed with diathermy and the dissection of the axillary part as a sharp dissection. The incidence of intraoperative bleeding and the duration of surgery were registered. All patients underwent insertion of a closed suction drain. The drain was maintained on negative suction and removed when the daily drainage volume was below 30 ml. Compression dressing was applied for 48 h, and early arm exercises were advised for all patients. All patients were followed up postoperatively for registration of the total drainage volume until drain removal, for timing of drain removal, for the incidence of seroma formation, and for the management of seroma.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA) for analyzing the collected data. Qualitative data were described using number and percentage. Comparison between different groups with respect to categorical variables was made using the χ^2-test. Quantitative data were described using mean and SD for normally distributed data. Comparison between two independent populations was made using the independent *t*-test, and for more than two populations the *F*-test (analysis of variance) was used. Significance of the obtained results was judged at the 5% level.

Results

The study included 80 female patients who were randomly allocated to two groups; each included 40 patients. Patients in group I received general anesthesia with hydrocortisone, whereas patients in group II received general anesthesia without hydrocortisone. As regards the distribution of the studied patients based on age, tumor stage, and duration of surgery, no significant differences were observed between the two groups but there was a significantly lower total drainage volume in group I and the drain was removed earlier. As regards the incidence of postmastectomy seroma, only two patients had postmastectomy seroma in group I, whereas eight patients had postmastectomy seroma in group II, with a significant difference between the two groups (Table 1). Neither significant major intraoperative bleeding nor significant difference in wound infection rate and wound healing delay has been registered in either group.

Table 1 Distribution of the studied patients with respect to age, tumor staging, and perioperative data

Patient's data	Group I (n = 40)	Group II (n = 40)	P-value
Age	49.1 ± 10.2	48.0 ± 9.1	0.398
Tumor stage [n (%)]			
IIA	11 (27.5)	13 (32.5)	0.231
IIB	10 (25)	14 (35)	0.107
IIIA	12 (30)	11 (27.5)	0.521
IIIB	7 (17.5)	4 (10)	0.311
Duration of surgery	107.0 ± 11.3	104.8 ± 11.7	0.325
Total drainage volume	665.0 ± 107.5	871.4 ± 82.7	0.001*
Timing of redivac removal	9.5 ± 1.7	12.8 ± 2.0	0.009*
Incidence of seroma formation [n (%)]	2 (5)	8 (20)	0.005*

*Significant at $P \leq 0.05$.

As regards IL-6 and CRP serum levels, there was no significant difference between the two groups preoperatively (the baseline value), but postoperatively a significant decrease was observed in group I compared with group II (Table 2).

The relation between the incidence of postmastectomy seroma and the changes in IL-6 and CRP serum levels preoperatively and postoperatively showed that, with a greater decrease in IL-6 and CRP serum levels in group I, the incidence of postmastectomy seroma became lower than that in group II, with a significant difference between the two groups (Table 3).

The two patients who developed seroma in group I required two to three aspirations, whereas in group II eight patients had seroma — five of them required multiple aspirations and three patients needed a second tube drainage.

Discussion

Seroma can infrequently occur after any surgical procedure and is the most prevalent postoperative sequel after breast surgery, with an incidence of 10–85%, leading to significant morbidity and discomfort and possibly delaying the adjuvant therapy [16]. Different causes of seroma have been proposed, such as the disruption of lymphatic drainage with fibrinolysis, or the surgical technique, especially the use of electrocautery versus

Table 2 IL-6 and CRP measurement preoperatively and postoperatively among the studied patients

Measurement time	IL-6		CRP	
	Group I	Group II	Group I	Group II
Preoperative				
Minimum–maximum	35–130	53–120	0.7–1.8	0.9–1.8
Mean ± SD	135.8 ± 29.8	88.0 ± 13.9	1.24 ± 0.31	1.21 ± 0.30
t-test	0.393		0.172	
P-value	0.696		0.864	
6 h Postoperative				
Minimum–maximum	80–200	100–280		
Mean ± SD	135.8 ± 29.8	158.1 ± 40.8		
t-test	2.453			
P-value	P = 0.017*			
24 h Postoperative				
Minimum–maximum	50–150	95–260	1.2–3.0	1.8–3.2
Mean ± SD	107.6 ± 21.9	147.7 ± 39.8	1.91 ± 0.43	2.23 ± 0.40
t-test	4.912		3.806	
P-value	<0.0001*		<0.0001*	
Significance (preoperative/6 h postoperative)	P < 0.0001*	P < 0.0001*		
Significance (preoperative/24 h postoperative)	P < 0.0001*	P < 0.0001*	P < 0.0001*	P < 0.0001*
Significance (postoperative 6 h/24 h postoperative)	P < 0.0001*	P < 0.0001*		

CRP, C-reactive protein; IL-6, interleukin-6. *Significant at $P \leq 0.05$.

Table 3 Relation between the changes in CRP and IL-6 from baseline to 24 h postoperatively and seroma formation

Group	Seroma formation	Mean change in IL-6	*P*-value	Mean change in CRP	*P*-value
Group I	With seroma, *n* = 2	37.3 ± 11.02	0.003*	1.21 ± 0.698	0.001*
	Without seroma, *n* = 38	25.6 ± 10.3		0.789 ± 1.01	
Group II	With seroma, *n* = 8	72.6 ± 15.2	0.0001*	2.22 ± 1.22	0.006*
	Without seroma, *n* = 32	52.6 ± 11.3		1.03 ± 1.09	
Significance of seroma between two groups regarding		0.0013*		0.005*	

CRP, C-reactive protein; IL-6, interleukin-6; *Significant at $P \leq 0.05$.

knife dissection [17,18]. Oertli *et al*. [6] concluded that tranexamic acid given perioperatively and postoperatively at a dose of 1 g three times daily in a randomized double-blind trial can produce a significant reduction in the mean postoperative drainage volume as well as in the incidence of seroma formation; however, this may need postoperative patient compliance, which is not always secured as the patient usually prefers to be on a reduced medication load postoperatively; therefore, in our work we administered hydrocortisone at 100 mg at induction, followed by a second dose 2 h later, with no additional postoperative medication load. The efficacy of shoulder immobilization has been investigated by Knight *et al*. [5]. Although seroma resulted in a delay in return to normal shoulder mobility, no patient sustained a long-term musculoskeletal dysfunction. Retention of the drain *in-situ* for a longer period seems to be a logical measure as the formed seroma usually subsides with aspiration [19]. Estes and Glover [7] concluded that the suction drain left *in-situ* for a prolonged period maintains physical contact between contiguous surfaces so as to facilitate adhesion. In our work the drain was removed when the daily volume was below 30 ml. Conveney *et al*. [8] and O'Dwyer *et al*. [9] demonstrated that both drainage and seroma formation were significantly less when dead space was obliterated by suturing the skin flaps to muscle. A similar flap tacking procedure was advocated by Chilson *et al*. [20] as having proven value in seroma prevention. Lindsey *et al*. [21] applied topical fibrin glue in the operative site in a Sprague–Dawley rat model and similarly decreased the incidence of seroma following mastectomy. A seroma was traditionally considered an accumulation of lymphatic fluid [16]. However, it has been demonstrated that a seroma is more than a mere accumulation of serum, probably an inflammatory response forming a part of the initial phase of wound healing [22]. McCaul *et al*. [23] concluded that fluid collection after breast cancer surgery and axillary clearance reflects the exudative phase of wound repair. Schulze *et al*. [24] demonstrated that it was possible to inhibit the inflammatory response with a single preoperative infusion of high-dose steroid in patients undergoing open resection of the colon. Recently, impressive achievements in seroma treatment were described by Taghizadeh *et al*. [25]. The single-dose methyl-prednisolone sodium succinate level was set at 125 mg on the basis of results obtained from previous head and neck surgery studies [26]. However, the inflammatory response after mastectomy is probably more pronounced than that seen following head and neck surgery, and it seems that the failure to report a significant effect could be ascribed to a very low dose of glucocorticoid, or to the fact that glucocorticoid was administered very soon after surgery. The inflammatory response to heart surgery with cardiopulmonary bypass is much more pronounced than that of other types of major surgery, which may be because of excessive activation of inflammatory mediators that promote postoperative atrial fibrillation [26]. Several reports on cardiac surgery document a prophylactic effect of 15–30 mg/kg hydrocortisone intravenously 1 h before surgery and up to 0.3 mg/kg intravenously every 6 h for 3 days [27–29]. This may be the right schedule of glucocorticoid administration for seroma prophylaxis. Taghizadeh *et al*. [25] have reported the therapeutic use of 80 mg of triamcinolone (Kenolog; E.R. Squibb, Middlesex, UK) in patients with seroma formation after autologous latissimus dorsi breast reconstruction. The glucocorticoid was injected into the cavity immediately after seroma aspiration. They demonstrated that a single dose significantly reduced the need for any further aspiration, the total number of aspirations, the total volume aspirated, and the total time to dryness. In our study, we used hydrocortisone 100 mg at induction, followed by a second dose 2 h later. Further studies are needed to evaluate prophylactic anti-inflammatory regimens against therapeutic regimens. A previous study has shown that a high preoperative single dose of glucocorticoid infusion (30 mg/kg methyl-prednisolone sodium succinate) inhibited the normal IL-6 and CRP response after colonic resection, and reduced plasma cascade system activation, the inflammatory response, and the immunofunction, but had no detrimental effect on wound healing [30]. Others [25] have argued that glucocorticoid suppresses the inflammatory process by the formation of a phospholipase inhibitor lipocortin, which diminishes the supply of arachidonic acid available for prostaglandin and leukotriene synthesis. This results in the inhibition of capillary permeability, edema, migration of leukocytes, later signs of capillary proliferation, and fibroblast and collagen deposition. One of the side effects of corticosteroid administration is the risk of infection and complicated wound healing. We found no differences between the groups with respect to wound infection,

epidermiolysis, wound necrosis, and wound hematoma despite the significant difference between the two groups with respect to the changes in the inflammatory mediators, which is in accordance with other studies [24,26]. The present study demonstrated a lower total drainage volume during the postoperative period in the hydrocortisone group compared with the control group, with a significant difference. The significant difference in the total drainage volume had a significant effect on postoperative seroma formation as there was a tendency toward lower seroma formation rate in the hydrocortisone group compared with the control group, with significant difference. We also found that the drain was removed earlier in the hydrocortisone group compared with the control group, with significant difference. In the study by Okholm and Axelsson [30], the case material comprised patients undergoing different types of axillary surgery. Two-thirds of the patients in each group underwent surgery with an axillary clearance of levels I and II and one-third in each group only with sentinel lymph node biopsy. This difference in the type of axillary surgery could perhaps influence their results. One could argue that a mastectomy with a sentinel lymph node biopsy would yield a smaller postoperative inflammatory response because of a smaller surgical trauma, and thereby less formation of seroma. They included patients with both types of axillary surgery in the case material. In our study, we avoid this potential confounder by standardization of the technique as all of our cases were submitted to modified radical mastectomy with level I and II axillary clearance.

Conclusion

Postmastectomy seroma is likely a proinflammatory process and can be reduced by administering intravenous hydrocortisone on the induction of anesthesia and 2 h later, which significantly decreases the inflammatory mediators (IL-6 and CRP) whose perioperative changes significantly affect the incidence of postmastectomy seroma.

Acknowledgements

Conflicts of interest

None declared.

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