No effect of steroids on seroma formation after mastectomy

Mette Okholm[1] & Christen Kirk Axelsson[2]

ABSTRACT

INTRODUCTION: Seroma formation is a common problem after breast surgery. Studies indicate that seroma formation is a result of the postoperative inflammatory process. Glucocorticoid inhibits the inflammatory response.

MATERIAL AND METHODS: In a randomized pilot study, we measured the effect of glucocorticoid on drainage volume and seroma formation after breast surgery. A total of 42 patients with operable primary breast cancer scheduled for total mastectomy were randomized to either 125 mg methylprednisolone sodium succinate intravenously as a single bolus before the start of surgery or to a control group.

RESULTS: There was no difference between the groups as to the number of patients having drains from day to day. The drainage volume was lower in the methylprednisolone sodium succinate group than in the control group; however, the difference was not significant (7,979 ml versus 9,267 ml). There was a tendency towards a higher seroma formation in the methylprednisolone sodium succinate group, but the tendency was not significant (15,803 versus 13,987 ml), and there was no significant difference in the number of seroma aspirations after surgery (92 versus 99).

CONCLUSION: Injection of a bolus of 125 mg of methylprednisolone sodium succinate before mastectomy did not reduce drainage volume or seroma formation. If intravenous glucocorticoid did have an effect, the case material was too small to prove it.

Seroma formation is a common problem after breast surgery [1]. The pathophysiology and mechanism of seroma formation remains controversial and not fully understood. Kuroi et al [2] systematically reviewed the literature to identify risk factors for seroma formation. One meta-analysis, 51 randomized controlled trials, seven prospective studies and seven retrospective studies were identified. Obesity and a high drainage volume in the initial three days were found to be associated with high formation of seroma. The following factors had no significant influence on seroma formation: previous biopsy; hormone receptor status; stage; lymph node status and lymph node positivity; number of removed lymph nodes; number of drains; intensity of negative suction pressure; duration of drainage; removal of drains on the fifth postoperative day versus when the daily drainage volume was decreasing to a minimum; type of drainage (closed suction versus static drainage); immobilization of the shoulder; or use of fibrinolysis inhibitor. Some papers conclude that preventive measures have to be tailored to the individual patient and operative factors [3, 4].

The concentration of immunoglobulin G (IgG), leucocytes and granulocytes is higher in patients with seroma than in other patients [5]. Other factors like proteinases, proteinase inhibitors, different kinds of cytokines (tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), uPA receptor (uPAR), plasminogen activator inhibitor (PAI) -1, PAI-2, interleukin (IL)-6 and IL-1) are also found in the seroma fluid. This indicates that seroma is an acute inflammatory reaction during the first phase of wound repair, more so than a passive accumulation of serum [5, 6]. By paying attention to factors influencing the duration and intensity of the first phase of wound repair, it may be possible to prevent or to reduce the occurrence of seroma. Studies have shown that even a low steroid dose inhibited the postoperative inflammatory response. In several studies on head and neck surgery, oedema in the surgical area was reduced after a single dose of 125 mg methylprednisolone sodium succinate with no increase in surgical complications [7]. Even a larger single dose of glucocorticoid (30 mg/kg) used to reduce postoperative complications in abdominal surgery did not increase rates of surgical complications [7, 8].

On this basis, we raised the hypothesis that steroid administration would have a prophylactic effect on seroma formation. In a randomized pilot study, we measured whether a single dose of 125 mg methylprednisolone sodium succinate administered intravenously to breast cancer patients immediately before mastectomy would reduce the drainage volume or subsequent seroma formation.

MATERIAL AND METHODS

During a 12-month period, patients with operable primary breast cancer scheduled for mastectomy and axillary dissection and meeting the inclusion criteria of this study (**Table 1**) were included. Informed, written consent was obtained and the patients were randomized to

ORIGINAL ARTICLE

1) Department of Breast Surgery, Rigshospitalet, and 2) Department of Breast Surgery, Herlev Hospital

Dan Med Bul 2011;58(2):A4241

TABLE 1

Inclusion and exclusion criteria.

Inclusion
Women with operable primary breast cancer scheduled for mastectomy and axillary dissection
Exclusion
Men
Treatment with glucocorticoids within the past month
Pregnancy
Ischaemic heart diseases
Diabetes
Uraemia
Treatment with carbamazepin, phenytoin, phenobarbital, rifampicin, salicylats and ciclosporin
History with psychoses

the administration of glucocorticoid or no medical treatment; randomization was performed by means of sealed envelopes, prepared and numbered in random order by a consultant who did not participate in the study. The envelopes indicated to which group the patient belonged. If the patients were randomized to receive glucocorticoid, an intravenous injection of 125 mg methylprednisolone sodium succinate was given as a single bolus 1.5 hours before the start of surgery.

The study was planned as a clinical pilot study with drainage volume, seroma volume after removal of drains, number of punctures for seroma and wound complications as the end targets. Surgery was performed on 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. Axillary dissection was performed either by way of sentinel lymph node biopsy (SLNB), SLNB followed by axillary clearance of levels I and II, or axillary clearance of levels I and II only. All patients had one closed suction drain inserted through the medial end of the incision. The drain was removed when the daily volume was below 100 ml and the patient was discharged. No drains were left in situ for more than five days. Afterwards, seroma was aspirated, mainly by nurses, until the volume was below 50 ml clinically. The wound was controlled for wound infection and wound necrosis at every ambulatory visit. Wound infection was defined as redness with or without purulent seroma requiring antibiotic treatment. The final wound examination was done 14 days after the final seroma aspiration.

Statistics

For glucocorticoid treatment to gain a role in clinical practice, it must considerably reduce seroma formation. The pilot study was designed to show if this was the case. A reduction of seroma formation of about 70% with a two-sided significance level of 95% and 80% power would require about 20 patients in each group. A reduction of seroma formation of about 40% would, on the other hand, require 50 patients in each group. In this pilot study, we wanted to test if glucocorticoid could markedly prevent seroma formation, and we therefore chose to perform the study with 20 patients in each group. The Mann-Whitney test and Fiscer's exact test were used for comparison between groups. A level of 5% was considered significant.

RESULTS

In the study period, 80 patients fulfilled the inclusion criteria; due to protocol violations, 21 patients were never asked to participate and 11 patients refused inclusion. Therefore, a total of 48 patients were randomized. Afterwards, there were six dropouts as four patients were reoperated because paraffin sections showed micrometastasis in their sentinel node, one patient randomized to

TABLE 2

Patient characteristics.

	Methylprednisolone sodium succinate group	Control group	p value
Patients, n	20	22	–
Age, years, median (range)	63.2 (48-86)	62.3 (43-79)	NS
BMI, kg/m^2, median (range)	23.9 (16.0-36.0)	24.0 (20.4-31.1)	NS
Systolic blood pressure, mmHg, median (range)	159 (120-191)	159 (122-210)	NS
Diastolic blood pressure, mmHg, median (range)	87 (67-110)	91 (78-110)	NS
Mastectomy and SNLB, n	6	7	–
Mastectomy and SNLB and axillary clearance of level 1 and 2, n	5	8	–
Mastectomy and axillary clearance of level 1 and 2, n	9	7	–
Operation time, min., median (range)	125 (64-185)	133 (59-220)	NS
Peroperative bleeding, ml, median (range)	244 (40-500)	249 (48-560)	NS
Weight of tissue, g, median (range)	624 (75-1,234)	624 (115-2,115)	NS

BMI = body mass index; NS = non-significant; SNLB = sentinel lymph node biopsy.

TABLE 3

Drainage volume.

	Methylprednisolone sodium succinate group (n = 20)				Control group (n = 22)				
	drains, n	median, ml	mean, ml	total, ml	drains, n	median, ml	mean, ml	total, ml	p value
Day 1	20	250	240.3	4,805	22	265	286.0	6,292	NS
Day 2	11	70	76.3	1,526	13	92.5	80.2	1,765	NS
Day 3	7	0	51.8	1,035	9	0	35.0	770	NS
Day 4	4	0	27.0	538	2	0	11.0	240	NS
Day 5	1	0	3.8	75	0	0	9.1	200	NS
Total				7,979				9,267	NS

NS = non-significant.

the Control Group was re-operated on day three because of infection and suspicion of necrotizing faciitis, which was not confirmed. Finally, one patient randomized to the methylprednisolone sodium succinate group was treated with glucocorticoid day one after surgery due to an allergic reaction. The final study group thus consisted of 42 patients: 20 patients randomized to the methylprednisolone sodium succinate group and 22 patients to the control group. The two groups were identical in terms of patient characteristics such as age, body mass index (BMI) and blood pressure. Surgery characteristics like type of operation, operation time and peroperative bleeding were also similar in the two groups (**Table 2**).

In order to evaluate the possible effect of the steroid injection on fluid production, the postoperative course was divided into two periods: the fluid production in the period with drains (postoperative days 1-5) and the fluid production in the post-drain period, known as seroma. There was no difference between the groups in terms of the number of patients having drains from day to day (**Table 3**). The drainage volume was lower in the methylprednisolone sodium succinate group than in the control group; however, the difference was not significant (7,979 ml versus 9,267 ml) (Table 3).

In the post-drain period, four patients (9.5%) – two patients in each group – never developed seroma. All four patients underwent mastectomy with SLNB. There was a tendency towards higher seroma formation in the methylprednisolone sodium succinate group, but it was not significant (15,803 versus 13,987 ml), and there was no significant difference in the number of seroma aspirations after the operation (92 versus 99) (**Table 4**).

No patients developed haematoma, but five patients in each group developed wound infection and were treated with antibiotics, half of these had minor infections with only redness. Three patients in the methylprednisolone sodium succinate group exhibited a minor degree of wound necrosis compared with the four patients in the control group.

DISCUSSION

A previous study has shown that a high preoperative single dose of glucocorticoid infusion (30 mg/kg methylprednisolone sodium succinate) inhibited the normal IL-6 and C-reactive-protein response after colonic resection; reduced plasma cascade system activation, the inflammatory response and the immunofunction; but had no detrimental effect on wound healing [8]. Others [9] have argued that glucocorticoid suppresses the inflammatory process by formation of a phospholipase inhibitor lipocortin, which diminishes the supply of arachidonic acid available for prostaglandin and leukotriene synthesis. This results in inhibition of capillary permeability, oedema, migration of leucocytes, later signs of capillary proliferation, and fibroblast and collagen deposition.

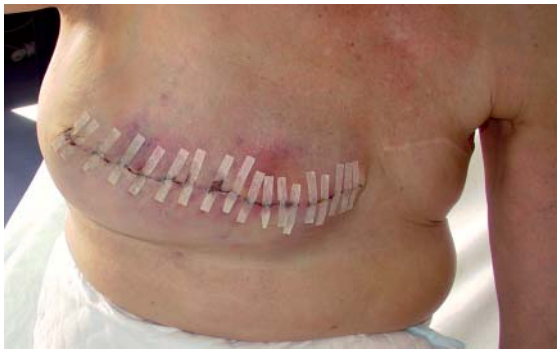
Two randomized studies have found a positive association between the drainage volume during the initial three postoperative days and seroma formation [10, 11]. The present study demonstrated a lower drainage volume during the initial two postoperative days and the full five-day period in the methylprednisolone sodium succinate group compared with the control group; yet, the difference was not significant. The small difference in the drainage volume had no effect on postoperative seroma formation; on the contrary, there was a tendency towards more seroma formation in the methylprednisolone sodium succinate than in the control

TABLE 4

Seroma formation.

	Punctures, n	Median volume, ml	p value
Methylprednisolone sodium succinate group (n = 20)	92	15,803	NS
Control group (n = 22)	99	13,987	NS

NS = non-significant.



Postoperative seroma.

group, but it fell short of significance. If it is accepted that the smaller drainage volume was a positive effect of glucocorticoid administration, then the higher level of seroma production could eventually be a rebound phenomenon.

The case material was composed of 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 SLNB. This difference in type of axillary surgery could perhaps influence our results. One could argue that a mastectomy with an SNLB would yield a smaller postoperative inflammatory response due to a smaller surgical trauma, and thereby less formation of seroma. However, according to general clinical experience, and as demonstrated in the present study, more than two thirds of the patients in each group operated with SNLB alone developed seroma. We therefore included patients with both types of axillary surgery in the case material.

The single dose methylprednisolone sodium succinate level was set at 125 mg on the basis of results obtained in previous head and neck surgery studies [7]. However, the inflammatory response after mastectomy is probably more pronounced than that which is seen following head and neck surgery, and it seems that the failure to report a significant effect could be ascribed to a too low dose level of glucocorticoid, or to the fact that glucocorticoid was administered too shortly after surgery. The inflammatory response to heart surgery with cardio-pulmonary by-pass is much more pronounced than that of other types of major surgery, which may be due to excessive activation of inflammatory mediators that promote postoperative atrial fibrillation [7]. Several reports on cardiac surgery document a prophylactic effect of 15-30 mg/kg hydrocortisone intravenously one hour before surgery and up to 0.3 mg/kg intravenously every six hours for three days [12-14]. This may be the right schedule of glucocorticoid administration for seroma prophylaxis. Lastly, it should be emphasized that the present study was designed to test a hypothetical 70% reduction of seroma, but no effect was found. If more patients had been included in the study, we might have detected a difference at the chosen dose of glucocorticoid.

Taghizadeh et al [9] have reported the therapeutic use of 80 mg of triamcinolone (Kenolog, E.R. Squibb, UK) on 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. Further studies are needed to evaluate prophylactic anti-inflammatory regimens against therapeutic regimens.

One of the side effects of glucocorticoid administration is the risk of infection and complicated wound healing. We found no differences between the groups regarding wound infection, epidermiolysis, wound necrosis and wound haematoma. This is in accordance with other studies [7, 8]. Moreover, suppression of the postoperative inflammatory process does not comprise a limitation on the use of higher or repeated doses of glucocorticoid.

We conclude that the hypothesis that seroma is reduced following intravenous glucocorticoid was not confirmed. If intravenous glucocorticoid did have an effect, this could not be demonstrated due to the limited size of the case material. On the other hand, recent reports seem to warrant future studies aimed at evaluating whether seroma formation could be prevented by induction of a higher preoperative steroid bolus, by intravenous steroid administration for two to three days, or by steroid administration directly into the operative field or by a combination hereof.

CORRESPONDENCE: *Mette Okholm*, Department of Breast Surgery, Rigshospitalet, Denmark, Blegdamsvej 9, 2100 Copenhagen Ø. Denmark.
E-mail: mette.okholm@rh.regionh.dk/mette_okholm@dadlnet.dk
ACCEPTED: 1 December 2010
CONFLICTS OF INTEREST: None
ACKNOWLEDGEMENT: The GCP Unit at Copenhagen University Hospital discussed the trial protocol and monitored the study.

LITERATURE

1. Gonzalez EA, Saltzstein EC, Riedner CS et al. Seroma formation following breast cancer surgery. Breast J 2003;9:385-8.
2. Kuroi K, Shimozuma K, Taguchi T et al. Evidence-based risk factors for seroma formation in breast surgery. Jpn J Clin Oncol 2006;36:197-206.
3. Agrawal A, Ayantunde AA, Cheung KL. Concepts of seroma formation and prevention in breast cancer surgery. ANZ J Surg 2006;76:1088-95.
4. Kuroi K, Shimozuma K, Taguchi T et al. Pathophysiology of seroma in breast cancer. Breast Cancer 2005;12:288-93.
5. Watt-Boolsen S, Nielsen VB, Jensen et al. Postmastectomy seroma. A study of the nature and origin of seroma after mastectomy. Dan Med Bull 1989; 36:487-9.
6. Baker EA, Leaper DJ. Proteinases, their inhibitors, and cytokine profiles in acute wound fluid. Wound Repair Regen 2000;8:392-8.
7. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg 2002; 195:694-712.
8. Schulze S, Andersen J, Overgaard H et al. Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch Surg 1997;132:129-35.

9. Taghizadeh R, Shoaib T, Hart AM et al. Triamcinolone reduces seroma re-accumulation in the extended latissimus dorsi donor site. J Plast Reconstr Aesthet Surg 2008;61:636-42.
10. Burak WE, Jr., Goodman PS, Young DC et al. Seroma formation following axillary dissection for breast cancer: risk factors and lack of influence of bovine thrombin. J Surg Oncol 1997;64:27-31.
11. Kopelman D, Klemm O, Bahous H et al. Postoperative suction drainage of the axilla: for how long? Prospective randomised trial. Eur J Surg 1999; 165:117-20.
12. Sauerland S, Nagelschmidt M, Mallmann P et al. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. Drug Saf 2000;23:449-61.
13. Fillinger MP, Rassias AJ, Guyre PM et al. Glucocorticoid effects on the inflammatory and clinical responses to cardiac surgery. J Cardiothorac Vasc Anesth 2002;16:163-9.
14. Halonen J, Halonen P, Jarvinen O et al. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. JAMA 2007;297:1562-7.