No effect of steroids on seroma formation after mastectomy

Mette Okholm & Christen Kirk Axelsson

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.
the administration of glucocorticoid or no medical treat-
ment; 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 be-
goed. If the patients were randomized to receive gluco-
corticoid, an intravenous injection of 125 mg methyl-
prednisolone 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 per-
formed on all patients using the same technique irre-
spective of their randomization. The dissection of mas-
tectomy flaps was performed with diathermy and the
dissection of the axillary part as a sharp dissection.
Axillary dissection was performed either by way of senti-
nel 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 in-
serted 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 as-
pirated, mainly by nurses, until the volume was below
50 ml clinically. The wound was controlled for wound in-
fec tion 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 cri-
teria; due to protocol violations, 21 patients were never
asked to participate and 11 patients refused inclusion.
Therefore, a total of 48 patients were randomized. After-
wards, there were six dropouts as four patients were re-
operated because paraffin sections showed micrometas-
tasis in their sentinel node, one patient randomized to

| 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, salicylates and ciclosporin
- History with psychoses

| TABLE 2 |

Patient characteristics.

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Methylprednisolone sodium succinate group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>63.2 (48-86)</td>
<td>62.3 (43-79)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m², median (range)</td>
<td>23.9 (16.0-36.0)</td>
<td>24.0 (20.4-31.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg, median (range)</td>
<td>159 (120-191)</td>
<td>159 (122-210)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg, median (range)</td>
<td>87 (67-110)</td>
<td>91 (78-110)</td>
<td>NS</td>
</tr>
<tr>
<td>Mastectomy and SLNB, n</td>
<td>6</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Mastectomy and SLNB and axillary clearance of level 1 and 2, n</td>
<td>5</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Mastectomy and axillary clearance of level 1 and 2, n</td>
<td>9</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Operation time, min., median (range)</td>
<td>125 (64-185)</td>
<td>133 (59-220)</td>
<td>NS</td>
</tr>
<tr>
<td>Peroperative bleeding, ml, median (range)</td>
<td>244 (40-500)</td>
<td>249 (48-560)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight of tissue, g, median (range)</td>
<td>624 (75-1,234)</td>
<td>624 (115-2,115)</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI = body mass index; NS = non-significant; SLNB = sentinel lymph node biopsy.
the Control Group was re-operated on day three because of infection and suspicion of necrotizing fasciitis, 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 group.

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Methylprednisolone sodium succinate group (n = 20)</th>
<th>Control group (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drains, n</td>
<td>Median, ml</td>
<td>Mean, ml</td>
</tr>
<tr>
<td>Day 1</td>
<td>20</td>
<td>250</td>
</tr>
<tr>
<td>Day 2</td>
<td>11</td>
<td>70</td>
</tr>
<tr>
<td>Day 3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Day 4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Day 5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>7,979</td>
<td></td>
</tr>
</tbody>
</table>

NS = non-significant.

### TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Median, ml</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone sodium succinate group (n = 20)</td>
<td>15,803</td>
<td>NS</td>
</tr>
<tr>
<td>Control group (n = 22)</td>
<td>13,987</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = non-significant.
Postoperative seroma.

The present study was designed to test a hypothetical hypothesis that seroma prophylaxis. Lastly, it should be emphasized that every six hours for three days [12-14]. This may be the effect of 15-30 mg/kg hydrocortisone intravenously one reports on cardiac surgery document a prophylactic effect that promote postoperative atrial fibrillation [7]. Several due to excessive activation of inflammatory mediators than that of other types of major surgery, which may be cardio-pulmonary by-pass is much 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 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 SLNB 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