The Prolonged Postoperative Analgesic Effect When Dexamethasone Is Added to a Nonsteroidal Antiinflammatory Drug (Rofecoxib) Before Breast Surgery

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BACKGROUND: Glucocorticoids provide analgesia. In this study, we evaluated the effects of adding dexamethasone to a multimodal postoperative analgesic regimen, including a long-acting nonsteroidal antiinflammatory drug.
METHODS: One-hundred patients admitted for ambulatory breast cancer surgery were studied. They received paracetamol 2 g and rofecoxib 50 mg orally 1 h before start of general anesthesia with propofol and remifentanil. The patients were then randomized to receive, in a double-blind manner, either dexamethasone 16 mg IV or placebo. Both groups received fentanyl 1 μg/kg IV and 20–40 mL bupivacaine 2.5 mg/mL wound infiltration before the end of surgery.
RESULTS: There was no difference in pain scores or rescue medication between the groups during the first 4 h after surgery. After discharge, the median pain score during coughing or shoulder movement was 3 on a 0–10 scale in patients receiving placebo, and 1 in the patients receiving dexamethasone, which did not reach statistical significance ($P = 0.06$). From 24 to 72 h, the median pain with coughing or shoulder movement in patients receiving placebo was 2, and 1 in patients receiving dexamethasone, which did reach statistical significance ($P < 0.05$). Forty percent of patients receiving dexamethasone were pain free from 4 to 24 h, compared with 24% of patients receiving placebo, a difference that did not reach statistical significance ($P = 0.09$). Similarly, 46% of patients receiving dexamethasone were pain free from 24 to 72 h, compared with 28% of patients receiving placebo ($P = 0.06$). More patients had slept poorly on the first night in the dexamethasone group than in the control group, 68% vs 44%, ($P < 0.05$).
CONCLUSIONS: Dexamethasone 16 mg provides prolonged postoperative analgesia from 24 to 72 h after surgery when added to a multimodal regimen including nonsteroidal antiinflammatory drug (rofecoxib).
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Tissue and cell destruction during surgery results in activation of enzymes responsible for synthesis of prostaglandins and other potent activators of pain, both at the site of injury and via blood-borne and neurogenic mediation to the central nervous system. Inhibition of the cyclooxygenase (COX) enzyme by drugs such as paracetamol and nonsteroidal antiinflammatory drugs (NSAIDs), including COX-II selective NSAIDs ("coxibs"), is well established as an important and effective way of diminishing postoperative pain (1). Glucocorticoids are inhibitors of both phospholipase and COX-II, as well as having numerous other cellular actions (2–4). As these enzymes are important in the synthesis of prostaglandins, glucocorticoids also have an analgesic effect, demonstrated in the dental pain model by Skjelbred and Lokken (5) and later confirmed by others (6–11).

Paracetamol, NSAIDs, and glucocorticoids have a ceiling of analgesic effect, not being sufficient as monotherapy after extensive surgery. However, even in this setting, they have an opioid-sparing effect, thus reducing the incidence and severity of opioid-mediated side effects (12). Additionally, the combination of paracetamol and NSAID will provide better analgesia than either drug given alone (13). As glucocorticoids act on the prostaglandin system differently than NSAIDs, and have other antiinflammatory effects, there may be better analgesia when glucocorticoids are added to NSAIDs. To our knowledge, this has been suggested in a few studies on dental surgery (14–16), but has not been tested in other clinical settings of postoperative pain.

For this reason, we tested whether adding a glucocorticoid, dexamethasone, to a combination of paracetamol and a COX-II selective NSAID, rofecoxib,

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for postoperative pain prophylaxis improved analgesia after breast cancer surgery.

METHODS

After approval of The Regional Committee for Medical Research and written informed consent, 100 female patients were enrolled in this prospective, randomized, double-blind study. The patients were admitted for ambulatory breast cancer surgery expected to last for 1–2 h. Further inclusion criteria were age between 18 and 60 yr and ASA class I or II. The patients were excluded if they had psychiatric, neurological, or liver disease, diabetes, used regular medication with known or suspected sedative or analgesic effects, were excessive alcohol drinkers, or abused drugs. Any contraindication to NSAIDs, glucocorticoids, or other drugs planned for anesthesia was also an exclusion criterion. Zopiclone up to 7.5 mg orally the night before surgery was accepted; otherwise, intake of any sedatives or analgesics for the last 24 h was excluded.

The patients received oral paracetamol 2.0 g and oral rofecoxib 50 mg as premedication. In the operating room, the patients had standard monitoring: electrocardiogram, noninvasive arterial blood pressure, capnography, and pulse oximetry. A Ringer's acetate crystalloid infusion was continued throughout surgery. General anesthesia was induced and maintained by a total IV technique with infusions of remifentanil and propofol, the latter by the Diprifusor® target control system. The lungs were ventilated by oxygen-air mixture through a laryngeal mask to a eucapnic end-tidal CO_2. Fentanyl 1 μg/kg was given 10 min before the end of surgery, and the wound was infiltrated by 20–40 mL of bupivacaine 2.5 mg/mL.

Patients were randomized either to dexamethasone 16 mg (Group D) or an identical volume of saline (Group P, placebo) using a computer-generated list of random numbers. The syringes were drawn up by a nurse not participating in any other aspect of the study, and labeled with the patient number. Shortly after induction of anesthesia, the patients received study medication by IV bolus injection.

In the postanesthesia care unit and subsequent hospital course, patients received rescue analgesia with fentanyl 0.5 μg/kg IV upon request, and metoclopramid 20 mg IV in case of retching, vomiting, or nausea for more than 10 min. The patients were regularly asked to report side effects and were tested for fulfillment of routine discharge criteria: ability to mobilize, ability to drink, clearheadedness, lack of nausea or significant pain. They were discharged to home or hospital hotel after 4 h observation in the hospital, or later if discharge criteria were not fulfilled. By 4 h postoperatively, the patients gave a global evaluation of satisfaction, side effects, and average pain experienced during the recovery period on a 0–4 scale (0 = none, 1 = slight, 2 = medium, 3 = much, 4 = maximal possible pain).

After discharge, the patients were instructed to use only oxycodone 5 mg orally when needed for extra analgesia throughout the 3 days of the study period.

The next day, 24 h after end of surgery, the patients filled in a written questionnaire asking for: strongest pain during a provocation maneuver in the period after discharge (coughing and stretching of shoulder) (Visual Analog Scale (VAS) scale 0–10), average pain (VAS scale 0–10), fraction of time spent with pain (0 = none, 1 = occasionally, 2 = half the time, 3 = most of the time, 4 = all of the time) and need of rescue medication. They were asked about any nausea, vomiting, or other complaints, as well as fatigue and amount and quality of night sleep. They were asked about daily activities such as drinking, eating, and mobilization out of bed. They were also asked about the need for help from relatives or professional caregivers, and their overall postoperative experience compared with their expectations.

At 72 h, the questionnaire was repeated, asking the same questions during the 24–72 h postoperative period.

For estimation of the sample size we calculated that 75% would have pain (VAS of more than 0 on a 0–10 scale) during the first 24 h after discharge in the placebo group and a reduction to 50% would be of practical and clinical interest. With a possibility of a two-sided outcome, a significance level (P) of 0.05 and a power of 0.80, a minimum of 45 patients in each group would be necessary to detect this difference.

Demographic variables with continuous data were compared with independent sample t-tests after checking for normal distribution in the data set. For other variables nonparametric testing with Mann-Whitney test or χ^2 test with Yates correction were applied. Most data are reported as median (range) or n (%) if not stated differently. A P value of 0.05 or less was considered statistically significant.

RESULTS

One-hundred consecutive patients consented to participate in the study. There were no drop-outs. All patients answered the 24-h questionnaire. Ninety-nine patients answered the 72-h questionnaire. The patient characteristics were similar between groups (Table 1) except for longer duration of surgery and a tendency of more extensive surgical procedures in Group D. There were no significant differences between the groups in preoperative risk factors for nausea (i.e., nonsmoking status, previous travel sickness or postoperative nausea and vomiting) or pain (i.e., preoperative pain, pain or analgesics last week), or in pre- or perioperative medication (data not shown).

There were no significant differences between the groups in pain, need for rescue analgesics, or side effects during the first 4 h postoperatively, or at discharge readiness. By 4 h, 77% of the patients were discharge ready and discharged from the hospital,

Table 1. Patient Characteristics (Mean ± SD)

	Group D (n = 50)	Group P (n = 50)
Age (yr)	53 ± 10	52 ± 11
Weight (kg)	69 ± 8.7	69 ± 10
Height (cm)	168 ± 5.0	168 ± 6.0
Duration of surgery (min)	84 ± 44*	70 ± 28
Type of breast surgery (n):		
Ablation	2	5
Breast excision/ablation + sentinel node	28	31
Breast excision/ablation + axillary lymph node dissection	12	7
Plastic surgery	4	3
Plastic surgery with expander or implant	4	4

* $P < 0.05$, t-test.

Table 2. Postoperative Pain and Need of Analgesic Medication, % or Median (Range)

	Group D (n = 50)	Group P (n = 50)	P-value
Postoperative, in hospital, 0–4 h			
Pain free	18%	22%	>0.1
Average pain, verbal scale (0 = no pain → 4 = max pain)	1 (0–3)	1 (0–3)	>0.1
Dose of rescue fentanyl (μg)	75 ± 66	87 ± 69	>0.1
1. Postoperative day, 4–24 h			
Pain free	40%	24%	0.09*
Average pain, VAS 0–10	1 (0–8)	2 (0–8)	0.05**
Pain during provocation (coughing, shoulder lift), VAS 0–10	1 (0–9)	3 (0–8)	0.06**
Fraction of time spent with pain*** (0 = no → 4 = all)	1 (0–4)	1 (0–4)	0.10
Number of oxycodone rescue tablets (5 mg) taken (n)	1 (0–4)	2 (0–5)	>0.1
2. and 3. Postoperative day, 24–72 h (n = 49 in group D)			
Pain free	46%	28%	0.06*
Average pain, VAS 0–10	0 (0–6)	1 (1–10)	0.05**
Pain during provocation (coughing, shoulder lift), VAS 0–10	1 (0–9)	2 (0–10)	0.04**
Fraction of time spent with pain*** (0 = no → 4 = all)	1 (0–4)	1 (0–4)	0.05**
Number of oxycodone rescue tablets (5 mg) taken (n)	0 (0–5)	0 (0–5)	>0.1

* χ^2 test with Yates correction, ** mann-Whitney test.

*** Nonsignificant tendency of less time with pain in Group D for both test periods.

which was not significantly different between the groups (78% vs 76%, Group D and P, respectively).

There was significantly less postoperative pain upon provocation in Group D during day 2 and 3 (Table 2, Fig. 4). There was a nonsignificant tendency in Group D ($P < 0.1$) towards less average pain (Fig. 1), less pain upon provocation (Fig. 2), and more pain-free patients in the 4–24 h postdischarge period, and similarly for average pain (Fig. 3), time spent with pain and number of pain-free patients during day 2–3 (Table 2).

There were no differences in the activities of daily living after discharge from the postanesthesia care unit (data not shown).

No serious side effects were observed. Nausea occurred in 20% of patients during the first postoperative 4 h in both groups (Table 3), with a nonsignificant tendency towards less nausea and vomiting after discharge in the dexamethasone group. During the first 24 h, there was a nonsignificant trend towards fewer patients reporting fatigue in Group D, 10% vs 24% in Group P ($P = 0.11$). More patients in the dexamethasone group reported reduced sleep than in the placebo group, 68% vs 44%, ($P < 0.05$) (Table 2). There was no significant difference in pain occurrence during the night: 18% of the dexamethasone patients reported pain during the first night, compared with 13% in the placebo group (ns) (Table 3).

DISCUSSION

This study shows a significant benefit for postoperative analgesia during the 24–72 h period after breast surgery from a single dose of dexamethasone 16 mg IV. The analgesic effect of dexamethasone supplementation of paracetamol, NSAID (rofecoxib), and local wound infiltration was evident at 72 h after surgery.

The postoperative analgesic effect of glucocorticoids has been well documented by many studies (5–11,14,16–18). Compared with other analgesics, the onset of analgesic effect seems to be delayed. In our study, there was no effect during the first four postoperative hours, which would be about 5–6 h after IV administration during induction of anesthesia. This is consistent with previous reports of delayed analgesic effect. Aasboe et al. were not able to demonstrate any analgesic effect from 12 mg betamethasone until 3 h postoperatively (6). In the study of laparoscopic surgery from Coloma et al., the antiemetic effect of dexamethasone was more pronounced after discharge than in the immediate 3 h postoperative period (19).

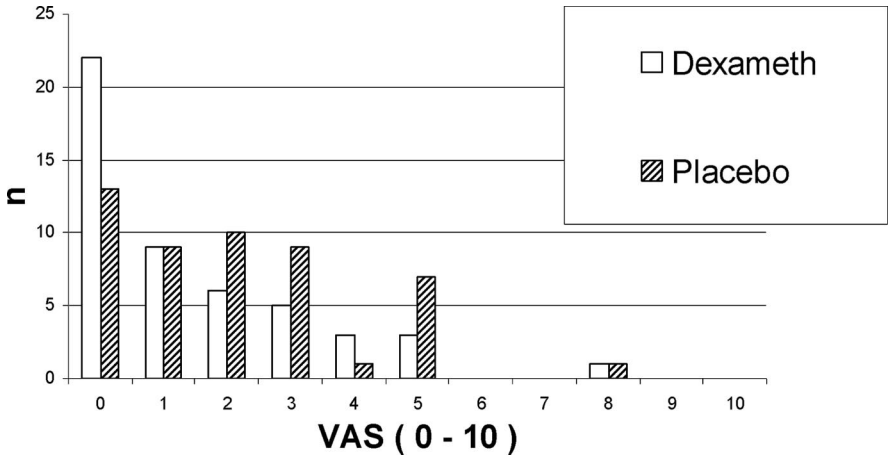

Figure 1. Average pain at rest, 4–24 hrs. n = number of patients, VAS = visual analogue scale. p = 0.052 between group dexamethasone and placebo (MW-test).

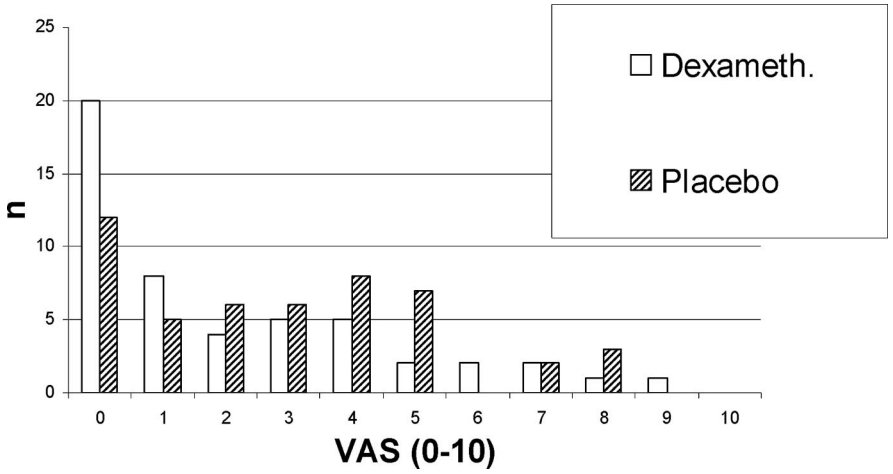

Figure 2. Pain score during provocation (coughing, shoulder lift), 4–24 hrs. n = number of patients, VAS = visual analogue scale. p = 0.065 between group dexamethasone and placebo (MW-test).

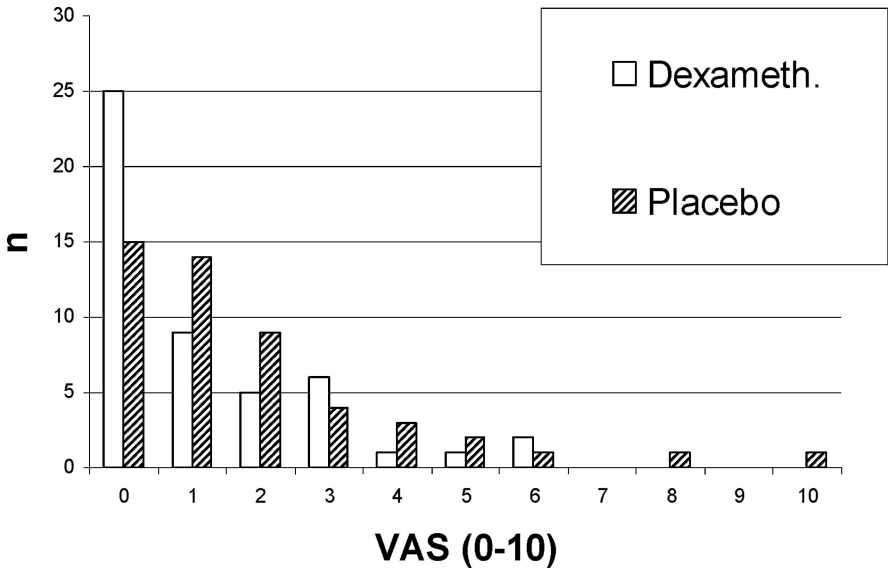

Figure 3. Average pain at rest, 24–72 hrs. n = number of patients, VAS = visual analogue scale. p = 0.050 between group dexamethasone and placebo (MW-test).

However, in a study from Romundstad et al., of 125 mg metylprednisolon IV postoperatively, the analgesic effect was evident at 60 min after administration when compared with placebo (10). There is also experimental and clinical evidence suggesting that glucocorticoids may have membrane actions that are more rapid than their effects on transcription (4).

Our results suggest that the duration of analgesic effect is prolonged after a single dose of IV dexamethasone. We observed significant effect for 3 days after administration, which was the last data point recorded. In a previous study by Romundstad et al., a single dose of 125 mg metylprednisolon was also analgesic for 3 days (9). Bisgaard et al. reported

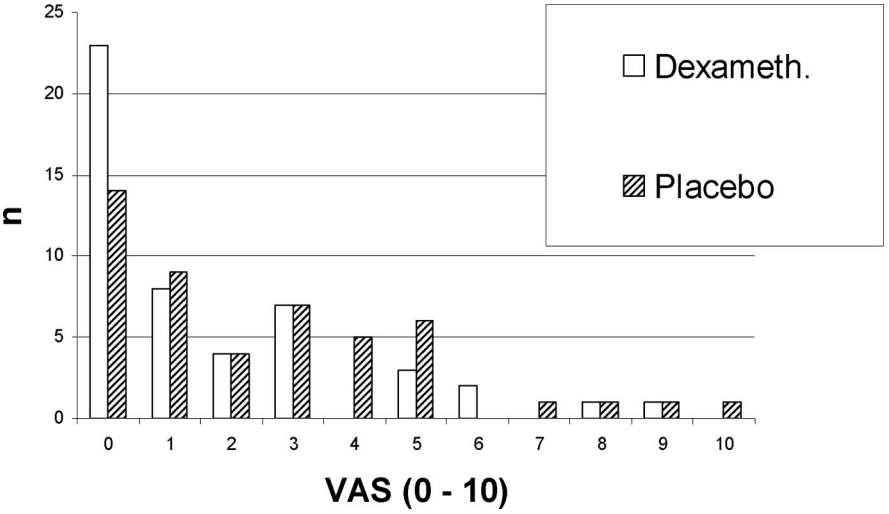

Figure 4. Pain score during provocation (coughing, shoulder lift), 24–72 hrs. n = number of patients, VAS = visual analogue scale. p = 0.049 between group dexamethasone and placebo (MW-test).

Table 3. Postoperative Side Effects, n (%)

	Group D (n = 50)	Group P (n = 50)
Postoperative, in hospital, 0–4 h		
Nausea	10 (20%)	10 (20%)
Vomiting	0	0
1. Postoperative day, 4–24 h		
Nausea	6 (12%)	9 (18%)
Vomiting	1 (2%)	2 (4%)
Tired, fatigue	5 (10%)	12 (44%)
Reduced amount of night sleep	34 (68%)*	22 (44%)
Restlessness during night	21 (42%)	14 (28%)
Total experience worse than expected	4 (8%)	2 (4%)
2. and 3. Postoperative day, 24–72 h (n = 49 in group D)		
Nausea	3 (6%)	7 (14%)
Vomiting	0	1 (2%)
Tired, fatigue	5 (10%)	7 (14%)
Reduced amount of night sleep	17 (34%)*	16 (32%)
Total experience worse than expected	5 (10%)	2 (4%)

* $P < 0.05$ χ^2 test with Yates correction.

reduced pain through 1 wk after a single dose of dexamethasone 8 mg during laparoscopy (8). The plasma elimination half-life of dexamethasone is only about 6 h (20), suggesting a persistent drug effect unrelated to plasma concentration. Because glucocorticoids inhibit transcription (21), changes in protein expression can be expected to persist after the drug is cleared from plasma.

Rofecoxib was chosen as the NSAID for our study due to the prolonged analgesic effect of at least 24 h (22) and the widespread postoperative use at the time the study was initiated. However, as rofecoxib is presently not marketed due to side effects from long-term use, other NSAIDs should be tested in this context.

A problem with testing one effective analgesic regimen against another effective combination is the low power of the model to reveal differences, because both groups have adequate pain relief. This was evident in our study. Pain scores after discharge were mostly in the 1–3 range on a 0–10 scale, even during provocation. Still, there was a consistent tendency of *P*-levels of 0.05–0.1 for all tests of the dexamethasone patients to have less pain after discharge, although statistically significant only for provoked pain during days 2–3 and for pooled maximal pain scores during the whole 4–72 h period.

In conclusion, a single dose of 16 mg dexamethasone was shown to have a prolonged analgesic effect with delayed onset. The effect was in addition to the initial effect of NSAID (rofecoxib).

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