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*Published in:*  
Journal of Clinical Anesthesia

*DOI:*  
[10.1016/j.jclinane.2014.02.006](https://doi.org/10.1016/j.jclinane.2014.02.006)

2014

[Link to publication](#)

*Citation for published version (APA):*  
Olanders, K., Lundgren, G. A. E., & Johansson, A. (2014). Betamethasone in prevention of postoperative nausea and vomiting following breast surgery. *Journal of Clinical Anesthesia*, 26(6), 461-465.  
<https://doi.org/10.1016/j.jclinane.2014.02.006>

*Total number of authors:*  
3

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**Betamethasone in prevention of postoperative nausea and vomiting following breast surgery.**

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Key Words: postoperative nausea and vomiting, betamethasone, breast surgery

Running head: Steroid treatment and PONV.

**ABSTRACT**

**Study objective:** *To investigate whether betamethasone decreases the incidence of postoperative nausea/vomiting and reduces postoperative pain following partial mastectomy.*

**Design:** *Prospective randomized study.*

**Setting:** *Operating room, postanesthesia care unit.*

**Patients:** *Eighty (80) ASA physical status I and II women scheduled for elective breast cancer surgery.*

**Interventions:** *Patients were randomly allocated to one of two groups in a double-blind fashion, which resulted in 37 patients assigned to group B (betamethasone) and 38 patients to group C (control). Group B received 8 mg betamethasone intravenously before the start of surgery.*

**Measurements:** *The rate of PONV and pain using a numeric 0-10 rating scale (NRS), as well as rescue doses of antiemetics (ondansetron) and analgesics (ketobemidone).*

**Main results:** *There was a significant lower incidence of postoperative nausea (PON) scoring  $NRS \geq 1$  for the group B in the 4-12 hour period compared with the control group C ( $p=0.02$ ). The cumulative incidence of PON was 57% in the group B vs. 68% in the group C ( $p=0.27$ ). The overall incidence of postoperative vomiting (POV) was 18% and 20% in the betamethasone group (B) and control group (C), respectively. Postoperative pain was reduced by 40% for group B in the 4-12 hour period, but the mean dose of postoperative rescue analgesics did not differ between the groups.*

**Conclusions:** *Preoperative betamethasone reduces severity of PONV and pain in patients undergoing elective breast surgery.*

## INTRODUCTION

Breast surgery is often associated with a high incidence of postoperative nausea and vomiting (PONV), as well as pain. It has been shown that 47-68% of patients undergoing minor breast surgery, mastectomy and breast reconstruction suffer from PONV [1-3]. Troublesome pain and PONV may prolong recovery and hospitalization, and are some of the most common causes of hospital admission following ambulatory surgery [4]. Since postoperative nausea, vomiting and pain have a multifactorial pathophysiology, a multimodal approach of treatment usually is used today.

Glucocorticoids such as dexamethasone have shown to be a useful agent in a multimodal strategy decreasing both PONV and pain [5]. It has previously been found that ondansetron 4 mg and dexamethasone 4 mg are equally effective in the prevention of PONV following breast surgery [6]. The incidence of PONV was similar between the groups and was reduced to around 35%. This result agrees with our early findings of a standardized general anesthetic with a volatile agent combined with a low dose of fentanyl intravenously [7].

Betamethasone, a potent, long acting glucocorticoid steroid with anti-inflammatory and immunosuppressive properties, but no or little mineral corticoid activity, has only been investigated in a few previous studies for potential postoperative antiemetic or analgesic properties [8, 9]. Betamethasone has a plasma half life of 5 hours and a biologic activity in tissues of more than 48 hours. Betamethasone is commercially available, cheap and commonly used in our daily practice including conditions such as allergic reactions, asthma, cerebral edema, spinal injury, as well as adjuvant to other treatment of PONV.

Dexamethasone, with an equipotent anti-inflammatory and glucocorticoid effect as betamethasone [10], has been shown to cause reduction in the incidence of PONV with a plateau

effect at 8 mg [11], although other studies have demonstrated significant effects with lower doses [12].

The purpose of this study was to investigate if betamethasone decreases the incidence of PONV and reduces postoperative pain following breast surgery.

## MATERIALS AND METHODS

Approval from the local ethics committee in Lund and the Medical Products Agency (MPA) in Sweden was obtained for the study protocol. Eighty (80) women with American Society of Anesthesiologists physical status I or II in the age group 18-65 years, scheduled for elective partial mastectomy, with or without axillary gland removal, gave written informed consent to participate in the study. The patients were not treated with cytostatic drugs preoperatively. Exclusion criteria were previous experiences of PONV or severe travel sickness, medication with corticosteroids or neuroleptics, known allergy to any of the study drugs, neurological disease or pregnancy. The patients were randomly allocated to one of two groups in a double-blind fashion, which resulted in 37 patients assigned to group B and 38 patients to group C. Group B (betamethasone) received 8 mg betamethasone intravenously before the start of surgery, whereas group C (Control) received no prophylaxis of PONV before surgery.

All patients were premedicated with 1 gram paracetamol orally 30 minutes before induction. Intravenous fluid with buffered 2.5% glucose solution was initiated in the operating room, starting with a bolus of 0.5 ml/kg bodyweight times the number of fasting hours, followed by continuous infusion rate of 150 ml/hour. Monitoring included ECG, pulse-oximetry and non-invasive blood pressure. General anesthesia was induced with intravenous glycopyrrolate 0.2 mg, fentanyl 0.5 µg/kg and propofol 2-2.5 mg/kg before inserting a laryngeal mask airway. Anesthesia was maintained with sevoflurane at an end-tidal concentration of 0.7 MAC in 40% O<sub>2</sub> + 60% N<sub>2</sub>O, using a fresh gas flow of one liter per minute. All patients maintained spontaneous breathing in a circle system with a carbon dioxide absorber. A second dose of fentanyl 0.5 µg/kg was given prior to skin incision and additional doses of fentanyl (0.5 µg/kg) were given if the

systolic blood pressure increased above the baseline level assessed at rest during the preoperative evaluation.

The nursing staff in the recovery room, blinded of the randomization, used a numeric 0-10 rating scale (NRS) for evaluating the degree of nausea and pain (from 0 = no nausea or pain to 10 = worst nausea or pain imaginable) starting at the patient arrival to the recovery room (time = 0) and then every hour the first six hours, followed by the time points 12, 18 and 24 hours postoperatively. If the pain intensity was  $\geq 5$  the patients received ketobemidone iv in doses of 1-2 mg until effect (pain intensity  $\leq 4$ ). All patients received 1 gram paracetamol orally every 6th hour. Nausea was treated with ondansetron 4 mg iv if the NRS intensity was  $\geq 5$ . The total dose of ketobemidone and ondansetron administered was recorded. Patients who were discharged before the end of the study period were contacted by telephone and asked about experiences of nausea, vomiting and pain using the same numeric rating scale.

### ***Statistics***

A power analysis with NRS scoring of nausea and pain as the primary variable revealed that a study population of 72 patients (36/group) was needed to detect a statistically significant difference at the 5% level. A clinical relevant difference of 1.0 on the numeric rating scale and an average SD of 2.0 reached with this sample size a power of 0.85 [13]. Data are presented as incidence, i.e. the percentage of patients, experiencing nausea or pain in the different time intervals. The Chi-Square and Fischer's exact test were used for statistical analysis of these parameters. The other data were analyzed using Student's *t*-test or the Mann-Whitney non-parametric test where appropriate and are presented as means and range.



## RESULTS

A total of eighty patients were included in the study of which five were excluded due to violation of the study protocol. Thirty-seven (37) patients were allocated to the betamethasone group (B) and 38 patients to the control group (C). All patients underwent breast sparing surgery, i.e. partial mastectomy (sector resection). Nineteen (19) patients in the betamethasone group and 23 patients in the control group also had up to 5 axillary glands removed (sentinel node). A full axillary gland dissection was performed on 8 patients in the betamethasone group and 7 patients in the control group. There were no differences in demographic data, number of smokers and duration of anesthesia between the groups (Table 1). The mean dose of fentanyl given intraoperatively was 75 (52-130) micrograms in group B and 77 (46-180) micrograms in the group C.

There was no statistical overall difference in the incidence of postoperative nausea or vomiting between the two groups studied. The cumulative incidence of postoperative nausea (PON) scoring NRS  $\geq 1$  at any time point studied was 57% in the betamethasone group (B) and 68 % in the control group (C) ( $p=0.27$ ). Furthermore, the cumulative incidence of PON with NRS  $\geq 3$  was 34 % in the betamethasone group (B) and 32 % in the control group (C). The overall incidence of postoperative vomiting (POV) was 18 % and 20 % in the betamethasone group (B) and control group (C) respectively.

When looking at the different postoperative time intervals there was a significant lower incidence of PON scoring NRS  $\geq 1$  for the betamethasone group (B) in the 4-12 hour period ( $p=0.02$ ). No differences were found during the 0-3 or 18-24 hour postoperative period (Table 2). Neither was any significant difference found between the groups during any postoperative time period for patients with PON scoring NRS  $\geq 3$ .

Twenty-nine percent (29%) of the patients in the betamethasone group (B) and 32 % in the control group (C) received at least one dose (4 mg) of rescue antiemetics with ondansetron. The incidence of PON (NRS  $\geq 1$ ) at each time point is shown in Fig.1 and in the different time intervals in Fig.2.

Although the experienced postoperative pain seemed to be lower in the betamethasone group, especially in the 4-12 hour period with a 40% reduction, the difference did not reach statistical significance in our study ( $p=0.22$ ) (Table 3). There was no difference in the mean dose of postoperative rescue analgesics with ketobemidone (group B;  $3.0 \pm 2.7$  mg versus group C;  $2.9 \pm 2.2$  mg).

## DISCUSSION

Betamethasone administered just before induction of anaesthesia has a small effect on postoperative nausea or pain following breast surgery.

This effect was observed in the 4-12 hour postoperative time period, which indicates that betamethasone has a slow antiemetic onset and that it possibly should be administered earlier prior to surgery in order to have effect in the early postoperative period. This is in line with previous studies using the closely structural related long acting glucocorticoid steroid dexamethasone, which have an analogous late antiemetic efficacy [5, 14]. Furthermore, the present study showed that an antiemetic effect only was detected when NRS levels for nausea was set as low as 1, which may be argued of its relevance in clinical practice.

The result was somewhat in conflict with other studies using dexamethasone [5, 15-16] or betamethasone [8] where a more convincing antiemetic and analgesic effect was observed. Nevertheless, a significant antiemetic effect was observed in the 4-12 hour postoperative period together with a 40% pain reduction in the same time interval, although the latter not statistical significant in our study. The antiemetic mechanism of action still remains unclear, but previous studies have excluded dopamine- and/or 5HT-3 antagonistic effects [17, 18].

One could argue whether the dose of 8 mg betamethasone in the present study was too low to show a significant effect, with the dose of 12 mg used in the study by Aasboe and co-workers in mind [8]. Nevertheless, a minimum effective dose of dexamethasone as low as 2.5 mg has been shown to reduce PONV [12]. On the other hand, a higher dose of glucocorticoids is probably needed to achieve a prolonged analgesic effect [19]. To this date no dose-response study on potential antiemetic and analgesic effect of betamethasone has been made.

As mentioned previously, the timing of the glucocorticoid administration is of importance, since the onset may be slow. Thagaard et al implicated that ketorolac, a non-steroidal anti-inflammatory drug (NSAID), was superior to glucocorticoids during the early postoperative period (0-4 hours), both in terms of less pain and less PONV, whereas glucocorticoids were equally effective as ketorolac in the later postoperative period (4-72 hours) [9]. We gave the betamethasone just before the induction of anesthesia because this was more applicable when the intravenous lines were established. Still there was only a small effect of postoperative nausea and pain in the 4-12 hour period and no obvious effect at later time points, which would have been anticipated with a later onset of betamethasone. The incidence of PONV and pain was low in the 18-24 hour period and it may have required a higher powered study in order to detect an effect of betamethasone.

Compared to other reports on breast surgery different surgical techniques, general anesthetics, and premedication make it difficult to compare postoperative PONV and pain scores between studies. There were several limitations in the present study. It is possible that a larger sample size as well as different anesthetic techniques may have revealed further differences between the groups. Our presented overall incidence of PON (32% with NRS  $\geq$  3) in the control group is notable low since patients in elective breast surgery who received no PONV prophylaxis demonstrated incidences between 40-50% using either a volatile anaesthetic- or total intravenous strategy. Our low doses of intravenous fentanyl are probably a confounding factor leading to a decreased incidence of PONV. Finally, some effect of betamethasone may be masked, due to the administered doses of rescue medications and the time intervals for documentation, given the highest incidences of PON and pain are noted in the early postoperative period. Early treatment with ketobemidone may have influenced the total incidence of pain throughout the study period.

This ambiguity together with the limitations mentioned above should stimulate further studies in this field.

In conclusion, preoperative betamethasone reduces PONV and pain in patients undergoing elective breast surgery.

**ACKNOWLEDGEMENTS**

The authors wish to thank the recovery room staff at the department of Intensive- and perioperative care, Lund University Hospital, for their invaluable help.

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## **Legends**

### **Table 1.**

Demographic data, presented as mean, range and relative frequencies.

### **Table 2.**

Incidence of postoperative nausea (PON) scoring NRS  $\geq 1$  and NRS  $\geq 3$  at different postoperative time intervals.).

### **Table 3.**

Incidence of postoperative pain scoring NRS  $\geq 3$  and NRS  $\geq 4$  at different postoperative time intervals.

### **Fig. 1.**

The cumulative incidence of postoperative nausea (PON) scoring NRS  $\geq 1$  at given time points (n=37, betamethasone vs. n=38, control).

### **Fig. 2.**

The incidence of postoperative nausea (PON) scoring NRS  $\geq 1$  at the different postoperative time periods (n=37, betamethasone vs. n=38, control).

*Table 1*

Patient demographics		
	Group B (Betamethasone)	Group C (Control)
Number	37	38
Age (Year)	53 (35-65)	55 (31-66)
BMI (kg/m <sup>2</sup> )	26,0 (18-40)	25,3 (16-38)
Smokers (%)	23	24
Duration of anesthesia (min)	95 (39-162)	97 (36-207)

*Table 2*

Incidence of postoperative nausea (PON)				
	NRS $\geq 1$		NRS $\geq 3$	
	Betamethasone (n = 37)	Control (n = 38)	Betamethasone (n = 37)	Control (n = 38)
0-3 h	57 %	58 %	32 %	26 %
4-12 h	23 % *	50 %	14 %	21 %
18-24 h	12 %	14 %	0 %	3 %
<b>Total</b>	<b>57 %</b>	<b>68 %</b>	<b>34 %</b>	<b>32 %</b>

*Table 3*

Incidence of postoperative pain				
	NRS $\geq 3$		NRS $\geq 4$	
	Betamethasone (n = 37)	Control (n = 38)	Betamethasone (n = 37)	Control (n = 38)
0-3 h	74 %	84 %	58 %	63 %
4-12 h	18 %	30 %	6 %	9 %
18-24 h	0 %	7 %	0 %	4 %
<b>Total</b>	<b>76 %</b>	<b>87 %</b>	<b>58 %</b>	<b>63 %</b>

Fig 1.

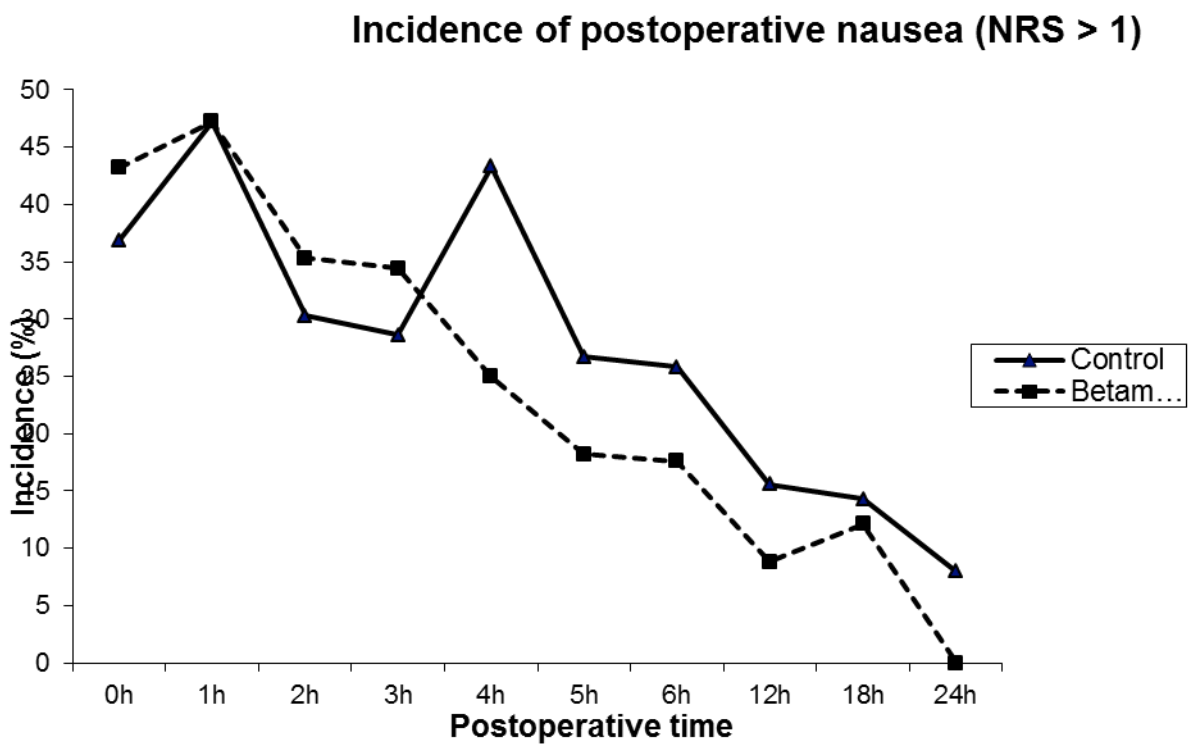


Fig 2.

