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A Double-Blinded Randomized Study

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Corticosteroids or not for postoperative nausea: A double-blinded randomized study

Running title: ERAS and Corticosteroids.

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Abstract

Background: Postoperative nausea and vomiting (PONV) is common after general anaesthesia, and corticosteroids are used in many protocols for Enhanced Recovery After Surgery (ERAS). However, surgical techniques are developing, and ERAS protocols need to be re-evaluated from time to time. In this study we compared the effects of oral vs. parenteral corticosteroid administration on postoperative nausea.

Patients and Methods: Elective Roux-y-gastric bypass (RYGB) patients were randomly assigned to either 8 mg betamethasone orally (n=50) or parentally (n=25) or as controls (n=25), in a double-blind design. PONV risk factors were noted. All patients had the same anaesthetic technique. Data were collected at baseline, on arrival to the recovery room (RR), and at five more time points during the first 24h. Nausea and tiredness were patient assessed using visual analogue scales; rescue drug consumption was recorded.

Results: Operation time was 30-40 minutes. Neither demographics nor risk factors for nausea differed between groups. Neither peak values for, nor total amount of, nausea differed between groups. The number of supplemental injections was the same for all groups.

Comments: In a setting of modern laparoscopic RYGB the value of betamethasone in preventing PONV seems to be limited. ERAS protocols may need re-evaluation.

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Background

The use of an Enhanced Recovery after Surgery (ERAS) protocol is a cornerstone in modern high-volume surgery. Much attention has been given to the problem of postoperative nausea and vomiting (PONV), and the preoperative administration of a corticosteroid is often included in such protocols. Internationally, the corticosteroid drug most commonly used for PONV prevention is dexamethasone [1, 2]. In reports on the efficacy of corticosteroids in bariatric surgery, parenterally administered dexamethasone has been used in multimodal therapies [3, 4, 5]. In Scandinavia betamethasone is often the drug used [6, 7]. In our previous ERAS protocol, the choice of betamethasone was based on a randomized study [8] where there was no difference between the two drugs in preventing PONV. There are no reports on the possible benefit of oral administration on PONV, and intravenous injections are more time-consuming and costlier than oral premedication. In comparison with surgery ten years ago, anaesthetic techniques have been refined, operative times have been reduced, laparoscopic instruments and cameras have been improved and also nursing skills in a high-volume unit have improved.

Aleris Obesity specializes in bariatric surgery, performing close to 2000 procedures per year. Our fast-track model includes a completely standardized operation, anaesthesia, and postoperative care, with our ERAS protocol central in treatment. This has led to a mean hospital time of 1.08 days, with 96 % of patients being able to go home on the first postoperative day [9]. However, in the light of the continuing development of surgery, ERAS protocols need constant development, and the present study aimed to examine one aspect of premedication: Can oral premedication with corticosteroids be equally effective as parenteral administration in reducing patient-experienced discomfort after laparoscopic RYGB during the first postoperative 24 hours, i.e. until discharge from hospital. Or could modern surgical

techniques obviate the need for corticosteroids? Primary endpoint was nausea, pain and tiredness were secondary.

Patients and methods:

All operations were performed at the Lund University-affiliated Aleris Obesity unit, Central Hospital, Kristianstad, Sweden. Sample size was based on results from a previous randomized pilot study of 50 patients where a slight difference between test subjects and controls in nausea rating was picked up at the 2% level [10]. Consecutive non-diabetic patients were recruited after informed consent from the lists for elective laparoscopic RYGB at Aleris Obesity. Randomization was performed on the morning of operation using closed envelopes in blocks of six. One test group of patients (n=50) received 8 mg betamethasone (Betapred®; Swedish Orphan Biovitrum, Stockholm) as tablets. Another group (positive controls, n=25) received betamethasone as an intravenous injection; both treatments approximately 1 hour before induction of anaesthesia. Another group (negative controls; n=25) was given no active corticosteroid substance. Patients in all three groups received both injection and tablets. Patient demographics are given in Table 1. Patients, surgeons and nurses at the ward were blinded to group belonging.

Collected variables: Information on risk factors for postoperative nausea were collected (smoking, history of motion sickness, previous PONV). Patients assessed their discomfort using 100 mm visual analogue scales (VAS; 0=no discomfort; 100 mm=worst imaginable)[11]. Base-line values were obtained 30-60 minutes before anaesthesia. Follow-up values were obtained on arrival to the recovery room and 2, 4 and 8 hours later. Final assessment was the following morning at 6 a.m., i.e. approximately 16 hours postoperatively.

Our ERAS protocol has been described previously [12, 13] and contains the following:

Routine medication before operation: All patients were routinely given 2 g acetaminophen p.o. (Alvedon®, GlaxoSmithKline) and 120 mg etoricoxib p.o. (Arcoxia®, MSD) preoperatively. Cefuroxime (Cefuroxim, Fresenius KABI, Sweden), 1.5 grams, was given as antibiotic prophylaxis.

Anaesthesia: Patients were operated between 8 a.m. and 2.00 p.m. All patients had identical anaesthetic technique, with propofol (Propofol®, Lipura, Sweden) and remifentanyl (Ultiva®, GlaxoSmithKline, Sweden) in a target controlled infusion, as previously described [11]. At the induction of anaesthesia were given: Atracurium 20 mg i.v. (Atracurium-hameIn®, Algol Pharma, Kista, Sweden), ketobemidon 10 mg i.v., (Ketogan®, Pfizer) and clonidine 22.5 micrograms i.v. (Catapresan®, Boehringer Ingelheim, Ingelheim am Rhein, Germany). No anaesthesia gases were used; propofol infusion was maintained until three minutes before completion of surgery.

Surgical procedure: A standard Roux-Y gastric bypass with a small, completely separated pouch, a 60 cm biliopancreatic limb and a 150 cm ante-colic, ante-gastric alimentary limb was performed in all patients as previously described [14] using 18 mm Hg intraabdominal pressure throughout the procedure. The mesenterial openings were closed.

Routine and on-demand medication after operation: Patients spent two hours in the recovery room (RR), where they usually received injections of 0.5-1 mg alfentanil (Rapifen®, Jansen Pharmaceuticals, Sollentuna, Sweden) and 0.5-1.0 mg droperidol (Dridol®, Prostrakan AB, Kista, Sweden). Patients were then transferred to the ward. There they received 1 g acetaminophen p.o. (Alvedon®, GlaxoSmithKline) every six hours, and an injection of 10 mg of oxycodone (Oxycontin®, Mundifarma AB, Göteborg, Sweden) at 8 p.m. on the day of operation. All patients were allowed sipping liquids immediately after surgery. In addition they received 1500-2000 mL Ringer's solution over an 18-20 hour time period. Mobilization

to a chair was initiated within one hour, and all patients had managed to stand within two hours.

Supplementary medication: If patients scored > 30 (of a possible 100) for nausea or pain, additional medication was offered. For nausea it was droperidol 0.5 mg i.v. or ondansetron 2 mg i.v. (Ondansetron®, B Braun), and for pain 10 mg ketobemidon. All such additional medication was recorded, if administered (Table 1). In addition, all patients started prophylaxis against deep venous thrombosis with the first injection 6-8 hours postoperatively (40 mg s.c. of enoxaparin, Klexane®, Sanofi, Sweden).

Statistics: All data are presented as mean (SE). Area-under-the-curve calculations were performed using GraphPad Prism 5 (GraphPad software, San Diego, CA). Distributions were analysed using Kolmogorov-Smirnov testing; differences between groups were calculated with two-tailed unpaired tests using Winstat for Excel® (Kalmia, NY, USA); differences with a p-value < 0.05 were considered significant.

Results:

In the study, 100 patients were initially included after informed consent. All operations were completed laparoscopically. There were no complications, and patients were discharged home on the first (n=93) or the second (n=7) postoperative day. No patient was readmitted. In the drop-out analysis, incomplete data were found for 1 or 2 patients in each group, so the final analyses were made on 95 patients (Table 1). Mean operative time was short (30-40 minutes) and consistent, with no differences between groups (data not shown). The prevalence of risk factors for PONV did not differ between groups (Table 1). In addition, there were no statistically significant differences between groups for number of rescue injections per person; 2.0 (0.4) for controls, 1.5 (0.3) for injection-treated and 2.2 (0.4) for orally pre-treated patients

(Table 1). A minority of patients were satisfied with our standard anti-pain medication, 22% in the control group, 31% in the orally treated group and 30% in those pre-treated with parenteral betamethasone; the numerical differences did not reach statistical significance. These patients needed no additional pain medication.

For the primary endpoint, patients scored nausea to be at its peak between 2 and 8 hours after surgery (Fig 1). No statistically significant differences were observed, neither between the two groups receiving active betamethasone, nor between saline-treated controls and either active group, at any point in time. Total amount of nausea in the time studied is expressed as the area under curve (AUC). No differences could be seen between groups (Figure 2). Nausea was reduced overnight but was still higher at 6 a.m. on the first postoperative morning compared with preoperative values ($p < 0.0001$).

Betamethasone injection caused a small but statistically significant reduction of tiredness vs. controls at one time point, viz. on arrival to the recovery room ($p=0.0054$), oral administration did not ($p=0.2012$). After that point in time, there were no other differences between groups receiving active treatment (Figure 3).

Discussion

Postoperative nausea and vomiting (PONV) is often a major determinant of time to discharge from hospital. When present, PONV renders postoperative nursing more difficult, and impairs patients' rapid return to oral alimentation. Premedication with corticosteroids has been used extensively in PONV prophylaxis. Such medication has been reported to be of value in several different types of surgery [2, 15, 16, 17]. Our previous ERAS protocol included parenterally administered corticosteroids since 10 years, and was based on literature studies as

well as one study from our own unit [8] The experience with preoperative corticosteroids in bariatric surgery is however limited [2, 5]. Most studies use dexamethasone as the corticosteroid and, importantly, as one part of multimodal treatments. Studies with the steroid as the independent variable are few. Hence it is difficult to ascertain the value of the steroid *per se*. Two separate Scandinavian studies have shown betamethasone to have favourable effects in preventing PONV [6, 7]. Thagaard et al found no significant difference between the effect on PONV in a randomized study comparing dexamethasone and betamethasone [8]. The present study was designed to study the efficacy of our current ERAS protocol and whether it was possible to change to a simpler, oral administration. We therefore examined the possible effects on PONV of a standard dose of betamethasone given orally or parenterally, in a setting of gastric bypass surgery. Non-diabetic patients were chosen since corticosteroids in this dose may affect blood sugar levels after surgery [5, 18]. The design chosen included a positive control as well as a placebo arm. Patients, surgeons and ward personnel were blinded to which treatment had been given. Sample size was determined from a previous pilot study comprising 25+25 patients [10] where there was a small but statistically significant advantage of oral betamethasone over control. Furthermore, we used continuous VAS data for the studied variables to improve statistical analysis, and not just the presence or absence of PONV. This technique is based on patients' self-reporting, it is well validated [11, 19] and has previously been used in studies on postoperative discomfort [e.g. 8, 20, 21].

We found no differences in the effect on nausea, neither for parenteral nor for oral administration over placebo control. This might be due to a power problem of the study, though our samples and dosages were equivalent to what has previously been used in the literature [6, 8]. Also, the power analysis was based on a pilot study from our own practice where the same design was used in a study on postoperative nausea in 50 randomized subjects [10]. Another possibly contributing factor may be that the level of nausea was low also in the

placebo-treated control group, with a peak average of only around 20 on a 100 mm scale, and few rescue injections had to be given. Our short operating times and modern anaesthetic techniques may, at least in part, explain these low levels of nausea. A correlation has been reported for shorter operating times giving lower levels of nausea [22]. On the other hand, Aasboe *et al* [6] found a positive effect of betamethasone in ambulatory surgery patients, with operations lasting only 25-35 minutes, even shorter times than in the present study. Our findings suggest that also type of surgery and/or non-pharmaceutical measures may be of importance in the prevention of PONV.

The single point in time where groups differed was in tiredness on arrival to the recovery room. At that one time point, patients that had received injected betamethasone reported significantly less tiredness than saline-treated control patients. We used only non-diabetic patients and administered only electrolyte solutions during the time of the study. The observed effect could well be due to a short rise in blood glucose levels, in analogy to what has been previously reported [5, 18].

A limitation of the present study is thus that the results may not be applicable to other departments with other background conditions. But the importance of re-evaluating existing ERAS protocols is generalizable. Such updating can be recommended for other departments where surgical and anaesthetic techniques are improving.

The value of corticosteroids, in this study betamethasone, in preventing low-grade PONV seems to be limited or non-existent. Since betamethasone and dexamethasone have been found to be equally effective [8], similar results should be expected for dexamethasone. It can be concluded that since modern RYGB surgery in a specialized unit causes such low-grade nausea even in a placebo-treated control group, the need for the inclusion of corticosteroids in an ERAS protocol can be questioned. This is compatible with previous findings that shorter operating times cause less nausea [22]. Our findings underline the importance of continuous

monitoring and adjustment of ERAS protocols, to adapt to changes in surgical and anaesthetic techniques.

This study was approved by the Institutional review board and the Lund University Ethics committee, and performed after informed consent by all participants according to the principles of the Helsinki declaration.

Lena Nordin reports no conflict of interest

Anna Nordlund reports no conflict of interest

Andreas Lindqvist reports no conflict of interest

Hjörtur Gislason reports no conflict of interest

Jan L. Hedenbro reports no conflict of interest

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Table 1: Patient demographics. Mean (SE). Risk factors for PONV are smoking, history of motion sickness or previous PONV.

	Oral	Injection	Controls
n	49	23	23
Sex (M/F)	16/33	4/19	6/17
Age	44.2 (1.7)	45.0 (2.9)	40.5 (2.9)
BMI	38.7 (0.8)	39.0 (1.2)	41.9 (1.3)
Percentage with risk factor(s) for PONV	22%	30%	30%
Supplemental pain medication, number of injections	2.0 (0.11)	1.5 (0.3)	2.0 (0.4)
Supplemental anti-emetic medication, number of injections	1.4 (0.2)	1.1 (0.2)	1.4 (0.2)

Figure 1: Mean values for nausea (mm VA scale; maximum value possible is 100 mm) before surgery and during the first postoperative 16 hours. There were no statistically significant differences between groups at any point in time; the apparent differences are between Injection and Oral-treated groups at 2 hours ($p=0.0681$), and between Controls and Oral at 4 hours ($p=0.1138$).

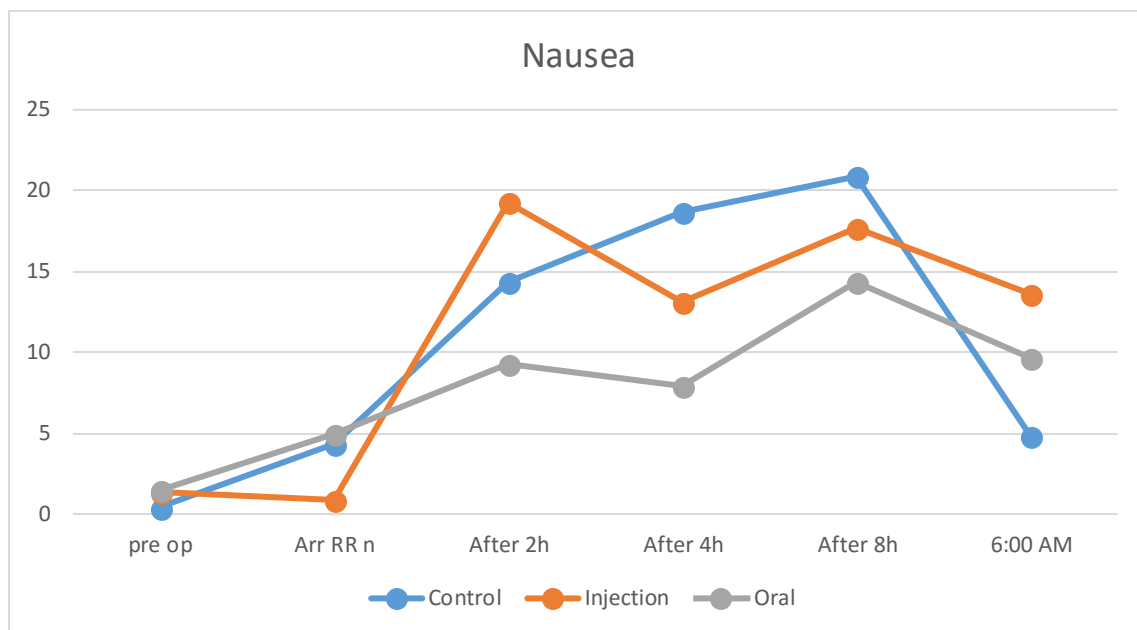


Figure 2: Total amount of nausea expressed as AUC (Mean, SE), from baseline to last point in time, 16 hours postoperatively. There were no statistically significant differences between groups (Inj. vs oral: $p=0.3807$)

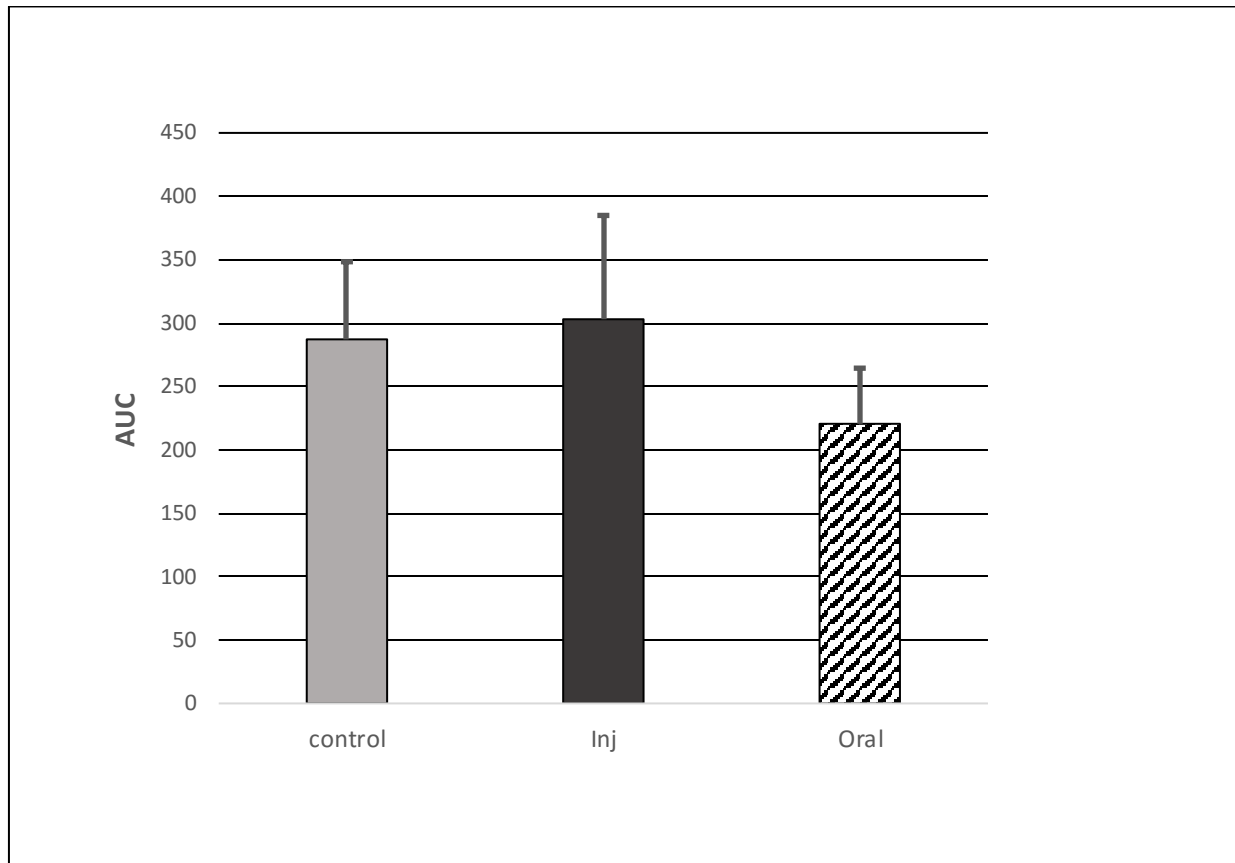


Figure 3: Mean values for tiredness (mm VA scale; maximum value possible is 100 mm) before surgery and during the first postoperative 16 hours. Values for parenterally treated patients were significantly lower than controls on arrival to the recovery room as indicated by *; ($p=0.0054$). There were no other statistically significant differences between groups at any point in time.

