

The Effect of Dexamethasone on Side Effects After Coronary Revascularization Procedures

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Corticosteroids decrease side effects after noncardiac elective surgery. We designed this randomized, double-blinded, placebo-controlled study to test the hypothesis that standard doses of dexamethasone (4 mg ×2) would reduce postoperative nausea, vomiting, and pain, decrease the incidence of atrial fibrillation (AF), and improve appetite after cardiac surgery, thereby facilitating the recovery process. A total of 300 patients undergoing coronary revascularization surgery were enrolled in this clinical study. The anesthetic management was standardized in all patients. Dexamethasone (4 mg/mL) or saline (1 mL) was administered after the induction of anesthesia and a second dose of the same study drug was given on the morning after surgery. The incidence of AF was determined by analyzing the first 72 h of continuously recorded electrocardiogram records after cardiac surgery. The patients were assessed at 24- and 48-h intervals after surgery, as well as at the time of hospital discharge, to determine

the incidence and severity of postoperative side effects (e.g., nausea, vomiting, pain) and patient satisfaction scores. Dexamethasone significantly reduced the need for antiemetic medication on the first postoperative day (30% versus 42%), and the incidences of nausea (15% versus 26%) and vomiting (5% versus 16%) on the second postoperative day ($P < 0.05$). In addition, dexamethasone significantly reduced the percentage of patients with a depressed appetite on the second postoperative day. However, the corticosteroid failed to decrease the incidence of AF (27% versus 32%) or the total dosage of opioid analgesic medication administered in the postoperative period. We conclude that dexamethasone (8 mg in divided doses) was beneficial in reducing emetic symptoms and improving appetite after cardiac surgery. However, this dose of the corticosteroid does not seem to have antiarrhythmic or analgesic-sparing properties.

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Corticosteroids have a variety of beneficial effects on recovery after elective surgery (1–4). A systematic review of the literature confirmed that dexamethasone reduces postoperative nausea and vomiting (PONV) (1). Corticosteroid therapy has also been reported to enhance appetite after major surgery (2). In patients undergoing noncardiac elective surgery, corticosteroids improved the management of postoperative pain (3) and facilitated the recovery process (4). In a retrospective study involving patients undergoing coronary artery bypass graft (CABG) surgery (5), large-dose

dexamethasone facilitated tracheal extubation within 6 h after surgery (26% versus 10%), but failed to reduce the length of stay in the intensive care unit (ICU) or hospital.

The most common postoperative side effect after CABG surgery is atrial fibrillation (AF), with a reported incidence of 20%–40% (6–9). In the previously mentioned study by Yared et al. (5) involving CABG patients at varying risks of developing AF, it was suggested that the administration of dexamethasone (0.6 mg/kg IV) reduced the incidence of new onset AF during the first 3 postoperative days from 32% to 19%. Furthermore, a recent publication by Fillinger et al. (10) demonstrated beneficial effects of a glucocorticoid (methylprednisolone) in suppressing the production of the inflammatory mediators interleukin-6 and interleukin-10 during and after cardiopulmonary bypass (CPB). In a study involving nonsurgical patients, Dernelis and Panaretou (11) reported that the inflammatory mediator C-reactive protein has a strong association with paroxysmal AF. It is therefore possible that

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the inflammatory response to CPB might contribute to the occurrence of new onset AF in the postoperative period. Of interest, a recent report by Cui et al. (12) suggested that the perioperative use of glucocorticoid steroids was associated with a small incidence (13%) of AF after heart transplantation. Although standard doses of glucocorticoids have been reported to be effective in reducing PONV after both cardiac (10) and noncardiac surgery (1,3,13), their effect on the incidence of AF has not been investigated.

Therefore, we designed a prospective, randomized, double-blinded, placebo-controlled study to test the hypothesis that the perioperative administration of 8 mg of dexamethasone in divided doses would reduce PONV, the severity of postoperative pain, as well as the incidence of AF in patients undergoing CABG surgery.

Methods

Patient Selection

The study was approved by the regional ethics committee for South-Eastern Norway. After written, informed consent, patients scheduled for elective CABG surgery were entered into this study. All patients receiving chronic corticosteroid medication and those with a history of AF (or other cardiac arrhythmias) were excluded from participating. The patients were randomly allocated to either a control (saline) or dexamethasone (8 mg IV) group. A block randomization scheme was used with 20 patients allocated to each block, to minimize the effects of any subtle changes in therapy during the course of the investigation. To maintain the double-blinded study design, the sealed envelope was opened immediately before surgery, and the study drug was prepared in identical-appearing syringes by a nurse who did not participate in the treatment of the study patients.

Anesthetic Management

All patients received morphine (10–15 mg IM) and scopolamine (0.4–0.6 mg IM) for premedication 30–60 min before arrival in the operating room. General anesthesia was induced with diazepam (7.5–10 mg IV), thiopental (3–5 mg/kg IV), fentanyl (4–6 μ g/kg IV), and pancuronium (0.1 mg/kg IV). Isoflurane (0.6%–1.2% inspired) and nitrous oxide (50%–60%) were administered for maintenance of anesthesia. The first dose of the study medication (either dexamethasone 4 mg IV, or saline 1 mL IV) was administered after initiating maintenance of anesthesia. All patients underwent median sternotomy and the operations were performed using CPB. Nitrous oxide was discontinued 5 min before CPB and isoflurane at the start of CPB when the patients received fentanyl (1–2 μ g/kg

IV) and midazolam (2 mg IV). Upon resumption of assisted ventilation, isoflurane (0.6%–1.2% inspired) was reintroduced. The patients were heparinized with an initial heparin dose of 400 IE/kg to achieve an activated clotting time of 480 s or longer, and protamine, 4 mg/kg IV, was administered after CPB to reverse the residual heparin effect.

Postoperative Management

All patients were tracheally extubated in the ICU when they were judged to be hemodynamically stable with adequate spontaneous ventilatory function. Nitroglycerin, labetalol, or nitroprusside was infused to maintain the systolic blood pressure <120 mm Hg in the early postoperative period. Upon arrival in the ICU, all patients received acetaminophen, 1 g PR, followed by 1 g every 6 h. Diclofenac 75–100 mg IM followed by 50 mg *per os* every 8 h was added unless contraindicated. Ketobemidone (an opioid analgesic) 1–2 mg IV was administered as a “rescue” analgesic when patients complained to the nurse about incisional pain in the postoperative period. On the morning of the first postoperative day, the patients received a second dose of the same study medication (i.e., dexamethasone 4 mg IV, or saline 1 mL IV). If the patient complained of feeling nauseated or experienced emetic symptoms (e.g., vomiting or retching), metoclopramide 10 mg IV was administered as the “first line” rescue antiemetic. If the emetic symptoms persisted, ondansetron 4 mg IV, droperidol 1.25 mg IV, and prochlorperazine 25 mg PR, were administered in a sequential manner. Blood samples were obtained at 6–12-h intervals for determination of plasma electrolyte and glucose levels.

Outcome Analysis

After removal of the chest tubes, the severity of pain was assessed using a visual analog scale, with 0 = no pain to 100 = most severe pain imaginable. The durations of nausea and pain were assessed using a standardized 5-point verbal rating scale: 0 = none, 1 = <50% of the time, 2 = 50% of the time, 3 = >50% of the time, and 4 = all the time. The patients were also asked to rate their appetite as normal or decreased (i.e., depressed). These assessments were performed on the morning of the first and second postoperative days, and at the time of discharge from the hospital. At the time of discharge (5–6 days after surgery), patients were asked to assess their level of satisfaction with their overall care, as well as the management of their emetic symptoms and pain using a 5-point verbal rating scale (with 1 = very bad to 5 = very good), and to record if they experienced any depressive symptoms, excessive thirst, difficult sleep, dysphoria, or

nightmares. The occurrence of AF during the postoperative period was assessed by reviewing the continuously recorded electrocardiogram (ECG) data from a Hewlett-Packard ECG monitoring system (H/P Vigilance, Stuttgart, Germany) during the first 72 h after surgery. Episodes of atrial flutter and supraventricular tachycardia were not included in the calculation of the relative incidences of AF. During the remainder of the hospital stay, the regularity of the patient's heart rate was assessed at 2-h intervals and ECG monitoring was reinstated if the patient displayed signs of a dysrhythmia. The number of patients who experienced an episode of AF and the duration of AF were both recorded.

The primary outcomes of this study were the incidences of PONV requiring a therapeutic intervention and new onset AF during the first 72 h after surgery. The secondary end-points were severity of pain and the opioid analgesic requirement. At the Feiring Heart Clinic, the database demonstrated incidences of both PONV and AF in the range of 30%–40% over the last 2 yr. Assuming that a reduction in AF from 35% to 20% would be of "clinical" significance, 145 patients would have to be enrolled in each treatment group to achieve a significant difference ($P < 0.05$) with a power of 80%.

Proportional data were presented as numbers or percentages in each group, whereas continuous data were presented as means \pm SD or medians (and interquartile ranges). Proportional data were evaluated using the χ^2 test. Two-sample t -test was used to make comparison between groups whenever criteria for normal distribution were accomplished, otherwise a Mann-Whitney U -test was applied. The Bonferroni correction was used for multiple comparisons between the groups. A P value < 0.05 was considered statistically significant.

Results

Three hundred patients were enrolled in this study over a period of 10 mo. Six were excluded from the efficacy analysis because of: 1) an anaphylactoid reaction to protamine ($n = 1$), 2) development of acute abdominal complications after surgery ($n = 2$), 3) a perforated ventricular ulcer ($n = 1$), and 4) protocol violations related to the use of nonapproved antiemetic drugs ($n = 2$). The two study groups ($n = 147$ in each) were comparable with respect to their demographic characteristics, pre- and intraoperative drug dosages, and surgical factors (Table 1). Perioperative blood loss, fluid balance, and recovery times in the two groups were also similar (Table 2).

In the dexamethasone group, there was a significant reduction in the number of patients receiving the primary rescue antiemetic medication on postoperative day 1 (30% versus 42%) and in the number of patients

experiencing nausea (15% versus 26%) and vomiting (5% versus 16%) on postoperative day 2 (Table 3). In addition, more patients in the control group had a decreased appetite on postoperative day 2 (45% versus 23%). However, the incidence (27% versus 32%) and mean duration (33 ± 31 versus 29 ± 33 h) of AF did not significantly differ between the dexamethasone and control groups, respectively (Table 4). Furthermore, there were no significant differences in the severity of postoperative pain as assessed by visual analog scale pain scores or the need for rescue analgesic drugs (Table 4). Finally, there were no differences in patient satisfaction during the early recovery period (data not reported). Interestingly, 10 patients in the dexamethasone group (versus none in the control group) experienced transient nausea immediately after injection of the second dose of the study drug ($P < 0.05$).

There were five postoperative infectious complications, three in the dexamethasone group (two pneumonias, and one urinary tract infection) and two in the control group (one mediastinal wound infection and one urinary tract infection) (Table 4). One patient in each study group died as a result of gastrointestinal complications (e.g., acute abdomen). None of the other patients in either group developed electrolyte disturbances, hyperglycemia, dysphoric, or acute psychotic reactions. All 294 study patients were discharged from the ICU on the first postoperative day and from the hospital on the fifth or sixth postoperative day.

Discussion

A small dose of dexamethasone administered during and on the morning after CABG surgery resulted in a significant reduction in emetic symptoms and improved appetite in this surgical population. These findings support the recent report by Fillinger et al. (10) in a similar patient population receiving methylprednisolone (15 mg/kg IV before surgery and 0.3 mg/kg IV every 6 hours for 24 hours). In the later study, the incidence of PONV in the first 24 hours after surgery was reduced from 33% to zero. The beneficial effect of corticosteroids on postoperative emetic symptoms after cardiac surgery is consistent with studies involving patients undergoing ambulatory surgery (3,13). Other possible explanations included the improved appetite in the dexamethasone group, consistent with the known anabolic effect of the corticosteroids (14). This may prove to be beneficial with respect to patient outcome because early oral feeding should facilitate recovery and rehabilitation (2). However, analogous to the study by Fillinger et al. (10), we also failed to demonstrate a significant beneficial effect of the glucocorticoid in facilitating the recovery process (e.g., tracheal extubation, ICU stay, or hospital discharge).

Table 1. Preoperative Demographic Characteristics and Intraoperative Data for the Two Treatment Groups

	Control (n = 147)	Dexamethasone (n = 147)
Age (yr)	64 ± 10	63 ± 11
Sex (M/F) (n)	120/27	114/33
Body surface area (kg/m ²)	27.1 ± 3.7	27.5 ± 3.8
Ejection fraction (%)	68 ± 12	69 ± 13
Perioperative risk score (Euroscore) (6)	3.0 ± 2.2	3.0 ± 2.3
History of postoperative emesis [n (%)]	11 (7)	10 (7)
Active smoker [n (%)]	33 (22)	33 (22)
Chronic medications [n (%)]		
β-Blocker	123 (84)	130 (88)
ACE inhibitor	44 (30)	46 (31)
Nitroglycerin	133 (90)	135 (92)
Insulin	8 (5)	5 (3)
Diuretic	21 (14)	15 (10)
Baseline systolic blood pressure (torr)	151 ± 28	153 ± 25
Diastolic blood pressure (torr)	74 ± 14	75 ± 12
Heart rate (bpm)	67 ± 14	68 ± 14
Baseline room air oxygen saturation (%)	96 ± 3	96 ± 3
Surgery time (min)	98 ± 27	102 ± 24
Cross-clamp time (min)	25 ± 10	27 ± 10
Extracorporeal circulation (min)	44 ± 15	46 ± 16
Peripheral anastomoses (n)	3.4 ± 0.8	3.4 ± 0.9
Central anastomoses (n)	1.5 ± 0.6	1.5 ± 0.6

Data are mean values ± SD, numbers (n), and percentages (%). There were no significant differences between the two groups.
ACE = Angiotensin-Converting Enzyme.

Table 2. Postoperative Recovery Characteristics for the Two Study Groups

	Control (n = 147)	Dexamethasone (n = 147)
Time to tracheal extubation (min)	149 ± 67	148 ± 69
Time to first oral intake (min)	378 ± 206	391 ± 236
Time to first dose of opioid analgesic (min)	165 ± 120	179 ± 122
Postoperative bleeding (mL)	744 ± 279	703 ± 247
Patients requiring blood transfusion [n (%)]	15 (10)	16 (11)
Fluid balance at end of surgery (mL)	+3066 ± 523	+2906 ± 489
Fluid balance at 24 h after surgery (mL)	+2749 ± 725	+2585 ± 855
Able to be mobilized [n (%)]		
Postoperative day 1	145 (99)	145 (99)
Postoperative day 2	142 (97)	144 (98)

Data are mean values ± SD, numbers (n), and percentages (%). There were no significant differences between the two groups.

The effect of corticosteroids on postoperative pain is controversial (3,4). Although a positive effect was reported by Aasboe et al. (3), this finding was not confirmed in a follow-up study involving a similar outpatient population (4). Fillinger et al. (10) also failed to find an effect of the glucocorticoid on postoperative pain scores or opioid analgesic requirements. One reason for the lack of analgesic effect in the current study may be attributed to the relatively low pain score in the control group because of the use of a "multimodal" analgesic regimen, making it difficult to demonstrate further improvement by adding the corticosteroid.

The failure to demonstrate a beneficial effect of dexamethasone on the incidence of postoperative AF seems to contradict the findings of Yared et al. (5). This earlier

study was a retrospective analysis in which there was no attempt to stratify the patients with respect to their risk of developing AF after CABG surgery (e.g., previous history of AF, poor left ventricular function, current therapy with β-blocking drugs). Furthermore, it is possible that transient episodes of AF could have been missed in the earlier study if the ECG was not continuously monitored for at least 72 hours.

The difference in outcome in the current study and the previous study by Yared et al. (5) may also be related to the larger dose of dexamethasone administered in the earlier study (0.6 versus 0.12 mg/kg). Alternatively, the reduction in the incidence of AF in the study by Yared et al. (5) may have been an "incidental finding" (albeit statistically significant) which

Table 3. Emetic Symptoms and Need for "Rescue" Antiemetic Drugs in the Two Study Groups

	Control (n = 147)	Dexamethasone (n = 147)
Postoperative day 1		
Any nausea symptoms [n (%)]	61 (42)	53 (36)
Nausea <50% of time [n (%)]	135 (92)	139 (95)
Emetic symptoms [n (%)]	32 (22)	25 (17)
Rescue antiemetic [n (%)]		
Metoclopramide	62 (42)	44 (30)*
Ondansetron	8 (5)	9 (6)
Droperidol	1 (<1)	1 (<1)
Prochlorperazine	2 (1)	1 (<1)
Appetite depressed [n (%)]	68 (46)	83 (56)
Postoperative day 2		
Any nausea symptoms [n (%)]	38 (26)	22 (15)*
Nausea <50% of time [n (%)]	139 (95)	142 (97)
Emetic symptoms [n (%)]	23 (16)	8 (5)*
Appetite depressed [n (%)]	66 (45)	34 (23)*

Data are medians (ranges), numbers (n), and percentages (%).
* Significantly different from the control group, P < 0.05.

Table 4. Postoperative Pain, Need for Analgesic Medication, and Side Effects in the Two Treatment Groups

	Control	Dexamethasone
Postoperative day 1		
Pain score (0-100)	37 ± 20	37 ± 18
Pain <50% of time [n (%)]	95 (65)	97 (66)
Analgesic medications		
Acetaminophen (g)	3.2 ± 0.6	3.1 ± 0.7
Ketobemidone (mg)	13 ± 7	13 ± 6
Diclofenac (mg)	26 ± 42	22 ± 45
Postoperative day 2		
Pain score (0-100)	33 ± 19	31 ± 19
Pain <50% of time [n (%)]	100 (68)	114 (78)
Analgesic medications		
Acetaminophen (g)	3.8 ± 0.5	3.9 ± 0.5
Ketobemidone (mg)	20 ± 8	22 ± 10
Diclofenac (mg)	14 ± 40	18 ± 45
Complications and side effects		
Atrial fibrillation [n (%)]	47 (32)	40 (27)
Surgical revision (n)	1	1
Urinary tract infection (n)	1	1
Pulmonary infection (n)	0	2
Wound infection (n)	1	0
Postoperative myocardial infarction (n)	1	3
Inotropic support at weaning from bypass (n)	0	1
Postoperative inotropic support (n)	2	2
Mortality (n)	1	1

Data are mean values ± SD, number (n), and percentages (%). There were no significant differences between the two groups.

would not be reproducible even if 40-60 mg of dexamethasone had been administered in the current study. Unfortunately, the more recent study by Fillinger et al. (10) did not evaluate the effect of perioperative methylprednisolone on the incidence of AF.

We were reluctant to use larger doses of dexamethasone (>0.12 mg/kg) because of possible side effects, including gastrointestinal and infectious complications, hyperglycemia, dysphoria, and psychotic reactions (15). Of interest, one patient in the control group died of complications associated with

an acute gastrointestinal perforation. In the studies by Yared et al. (5) and Fillinger et al. (10), the steroid-treated patients had larger blood glucose levels on admission to the ICU. However, there are no published data documenting an increase in clinically significant side effects after short-term administration of dexamethasone during the perioperative period (even when larger doses [>0.12 mg/kg] were administered).

Our data also suggest that the favorable effects of dexamethasone in limiting adverse gastrointestinal

side effects after cardiac surgery occur at smaller dosages than those alleged to produce an antiarrhythmic effect. Dose-ranging studies with dexamethasone are needed to carefully examine both the beneficial and potentially deleterious effects (e.g., immunosuppression, wound complications, hyperglycemia, dysphoria, psychotic reactions) of administering glucocorticosteroids to patients undergoing cardiac surgery. Our study can be criticized because it may have been underpowered to demonstrate significant differences in some of the other secondary outcome measures.

The incidence of AF is significantly reduced if β -adrenergic blocker therapy is continued after CABG (16,17). In our study, most of the patients (88% in the dexamethasone group and 84% in the control group) were receiving a β -adrenergic blocker immediately before surgery and these patients resumed using their β -adrenergic blocker after surgery. The incidence of AF in both study groups (27%–32%) is consistent with the incidence of AF after CABG surgery at most medical centers in the United States (5,10). An unexpected observation was the “acute” nausea spontaneously reported by 10 patients immediately after the IV injection of dexamethasone (4 mg) on the first postoperative day. Because this side effect has not been previously reported in the medical literature after IV injection of corticosteroid medication, it may be related to the solvent used in the commercial formulation [Decadron[®] (MSD)]. The “beneficial” effect of dexamethasone in reducing emetic symptoms and improving patient appetite, as well as potentially decreasing extravascular fluid (18), must be balanced against its potential side effects after CABG surgery.

In conclusion, dexamethasone (8 mg IV) reduced emetic symptoms and increased appetite after CABG surgery. However, the incidence of postoperative AF and the severity of pain were not altered.

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