

ORIGINAL ARTICLE

The influence of a prophylactic dose of dexamethasone for postoperative nausea and vomiting on plasma interleukin concentrations after laparoscopic cholecystectomy

A prospective randomised trial

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CONTEXT Little is known about the effects of small doses of dexamethasone used for the prophylaxis of postoperative nausea and vomiting on the innate host response.

OBJECTIVES We studied the influence of dexamethasone 4 mg on the perioperative plasma concentrations of interleukins after laparoscopic cholecystectomy. We hypothesised that there would be differences in pro-inflammatory interleukin concentrations in patients who received dexamethasone.

DESIGN A randomised controlled study.

SETTING University hospital.

PATIENTS Forty-six patients undergoing laparoscopic cholecystectomy under total intravenous anaesthesia were allocated randomly into one of two study groups; 42 patients completed the study.

INTERVENTIONS Patients in group 1 (dexamethasone, $n=22$) received dexamethasone 4 mg and group 2 ($n=20$) acted as controls.

MAIN OUTCOME MEASURES Plasma levels of tumour necrosis factor alpha and interleukins 1 β , 6, 8, 10 and 13 were measured before anaesthesia, before surgery and 2 and 24 h after surgery. The frequency and number of

episodes of postoperative nausea and vomiting were recorded.

RESULTS Areas under the curve of the percentage variation of interleukins 6 and 8 were significantly lower in the dexamethasone group. There were no significant differences between groups in the areas under the curve for tumour necrosis factor alpha and interleukins 1 β , 10 and 13. The greatest variation in interleukin concentrations was 2 h postoperatively, when the concentration of interleukin 6 was greater in the control group, whereas the concentration of interleukin 10 was higher in the dexamethasone group. Twenty-four hours after surgery, only the concentration of interleukin 6 remained significantly increased in both groups ($P=0.001$ and $P=0.002$, respectively). There were no significant differences between groups in respect of postoperative nausea and vomiting.

CONCLUSION Prophylactic dexamethasone given before laparoscopic cholecystectomy produced a significant decrease in concentrations of interleukins 6 and 8. Further studies are needed to investigate the clinical implications of these findings.

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Introduction

Dexamethasone is used commonly for prophylaxis against postoperative nausea and vomiting (PONV)¹ in doses ranging from 4 to 10 mg.^{2,3} Questions about the

clinical safety of a single dose of dexamethasone used for prevention of PONV have been raised. In a systematic review, Henzi *et al.*⁴ did not find evidence of any clinically

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relevant toxicity in otherwise healthy patients who received a single intravenous dose of dexamethasone 4 to 10 mg. A positive balance between benefits and risks after a single dose of dexamethasone has been reported by Jakobsson⁵ in a recent editorial review. However, there are even fewer studies on the effects of dexamethasone at a molecular level. Reports relating to cardiac surgery have shown that a single high dose of glucocorticoids (most often methylprednisolone) decreases concentrations of inflammatory interleukins (IL) IL-6, IL-8, tumour necrosis factor alpha (TNF α), C-reactive protein, complement and leukocyte receptor, and increases concentrations of IL-10.^{6–8} Similarly, leukocyte adhesion molecules are downregulated by steroid treatment,⁸ although some studies have shown that a single dose of either methylprednisolone or dexamethasone does not influence the plasma concentration of L-selectin or soluble vascular cell adhesion molecules (s-VCAM).^{9,10} The dose–response relationship still has to be determined because most of these studies used high doses of corticosteroids.

Therefore, it is still unknown whether a single low, prophylactic dose of dexamethasone has any influence on other components of the innate host response in humans. We have chosen the effects on interleukins because these are important markers of the inflammatory response with potential clinical effects. Thus, TNF α dysregulation is involved in cancer, inflammatory bowel disease and neurological disease progression,¹¹ whereas IL-6 is an acute phase response mediator. We considered that it would be of interest to investigate whether a dose of dexamethasone 4 mg has anti-inflammatory effects, thus explaining at least partly some of the beneficial clinical effects reported with a small dose of the drug, such as reduced postoperative pain¹² and more rapid postoperative recovery. In view of this, we set out to study the effects of a single dose of dexamethasone 4 mg used for prevention of PONV on the plasma concentrations of pro-inflammatory and anti-inflammatory interleukins during total intravenous anaesthesia (TIVA) for laparoscopic cholecystectomy.

We hypothesised that the circulating concentrations of the most powerful pro-inflammatory cytokines TNF α , IL-1 β , IL-6 and IL-8 in patients undergoing laparoscopic cholecystectomy and receiving dexamethasone would be lower than in patients who did not receive the drug. We chose a dose of 4 mg because this is the frequently recommended dose for prophylaxis against PONV and because we wanted to investigate to what extent anti-inflammatory effects could be found with such a small dose of dexamethasone. We selected laparoscopic cholecystectomy because this minimally invasive procedure had been reported in most studies to be associated with a reduced inflammatory response,^{13,14} although not all authors are of this opinion.¹⁵ A reduced inflammatory response of a small dose of dexamethasone might be an

argument in favour of extending the use of dexamethasone to other categories of patients and surgical procedures.^{5,8}

Patients and methods

Ethical approval for this study (IRB approval no. 178 B/2007) was provided by the Ethical Committee of the University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania (Chairperson Prof Dr F Loghin) on 19 December 2007. After obtaining written informed consent, 46 American Society of Anesthesiologists (ASA) physical status 1 or 2 patients scheduled for laparoscopic cholecystectomy under general anaesthesia (3rd Surgical Clinic, Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca) between January 2008 and August 2009 were allocated randomly to one of two study groups (23 patients to each group) using a computer-generated sequence. In the dexamethasone group, patients received dexamethasone 4 mg for prophylaxis against PONV; patients in the second group received no dexamethasone (control group). Patients with immune system disorders, known inflammatory diseases (including acute cholecystitis), an abnormal white cell count, asthma, obesity (BMI $\geq 30 \text{ kg m}^{-2}$), diabetes, gastric ulcer, allergies, history of PONV and current steroid or anti-inflammatory medication were excluded from participation. We used TIVA as an intervention for PONV prophylaxis,¹ taking into consideration the increased risk of PONV after laparoscopic cholecystectomy and the absence of PONV prophylaxis with dexamethasone in one of the study groups.

All patients received oral premedication of midazolam 7.5 mg. An intravenous cannula was inserted, blood was drawn for interleukin measurements and 500 ml of crystalloids were administered. This cannula was used as a dedicated line for fluid administration during anaesthesia and for blood sampling for subsequent interleukin measurements.

A second intravenous cannula was inserted for the infusion of drugs. Before induction of anaesthesia, dexamethasone 4 mg (1 ml clear solution) was given to patients in the dexamethasone group, and isotonic saline 1 ml was administered to patients in the control group. Anaesthesia was induced in all patients with a target-controlled infusion (TCI) of propofol with an initial target plasma concentration of $4 \mu\text{g ml}^{-1}$ (modified Marsh model) and a manually controlled infusion (MCI) of remifentanyl with $0.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$ in the first minute and then $0.25 \mu\text{g kg}^{-1} \text{ min}^{-1}$. Atracurium 0.6 mg kg^{-1} was administered to facilitate tracheal intubation. Anaesthesia was maintained with propofol at a rate sufficient to keep the bispectral index (BIS) level between 40 and 55 (SpaceLabs, St Gallen, Switzerland). Remifentanyl was adjusted in steps of $0.05 \mu\text{g kg}^{-1} \text{ min}^{-1}$ according to the patient's analgesic

needs and, if needed, additional aliquots of atracurium 10 mg were administered.

At the end of surgery, the infusions of remifentanyl and propofol were stopped and residual effects of atracurium were antagonised by administration of neostigmine with atropine.

Crystalloids were administered continuously throughout anaesthesia, and hypotension (defined as a decrease of mean blood pressure by greater than 25% of baseline values) was corrected with fluids and/or intravenous boluses of ephedrine 5 mg.

Postoperative analgesia included paracetamol 1 g orally every 8 h and pethidine 0.4 to 0.5 mg kg⁻¹ intravenously at the patient's request or when the pain score on a 5-point visual analogue scale (VAS, 5, worst pain possible; 0, no pain) was at least 3.

If present, PONV was treated with intravenous metoclopramide 10 mg, and ondansetron 4 mg if metoclopramide was not effective. The severity of PONV was not assessed in this study.

Interleukin measurement

Blood samples (7 ml) for interleukin measurements were drawn from the dedicated intravenous cannula at the following times: immediately after inserting the first peripheral cannula (T1), after tracheal intubation but before the start of surgery (T2), 2 h after recovery (T3) and 24 h (T4) after anaesthesia.

After centrifugation of the blood samples at 2500 rpm for 10 min at room temperature, separated plasma samples (3 to 4 ml) were stored into cryotubes at less than -20°C until the interleukin assays were performed. The interleukin assays were performed in one laboratory by the same team for all patients; the laboratory staff were not aware of the study group and were not involved in the patients' anaesthesia.

Plasma concentrations of both pro-inflammatory and anti-inflammatory interleukins were measured by commercially available ELISA kits (Quantikine, R&D Systems, Minneapolis, MN). Determinations employed the quantitative sandwich enzyme immunoassay technique. mAbs specific for interleukins had been precoated onto specific wells on ELISA plates. Standards and plasma samples were then pipetted into the wells of the plate, wherein cytokines are bound by the capture antibodies. An enzyme-linked mAb specific for each determined interleukin was added to each plate after washing the plate to remove the unbound antigen. A new wash was done to remove any unbound antibody-enzyme conjugates and a substrate solution was then added to the wells leading to a blue colour product that changed colour to yellow when the stop solution was added.

The optical intensity of the colour measured is proportional to the amount of plasma interleukin initially bound. The sample values are then read from a standard curve.

The minimum detectable concentrations as given by the manufacturer were as follows: less than 1 pg ml⁻¹ for IL-1β; less than 0.7 pg ml⁻¹ for IL-6; less than 1.5 pg ml⁻¹ for IL-8; less than 0.5 pg ml⁻¹ for TNFα; less than 3.9 pg ml⁻¹ for IL-10; and less than 32 pg ml⁻¹ for IL-13, with intra-assay and inter-assay coefficients of variation both less than 10%.

Normal plasma concentrations of interleukins measured with the Quantikine assays are in the following ranges: IL-1β, 1.0 to 3.9 pg ml⁻¹; IL-6, 0.7 to 12.5 pg ml⁻¹; IL-8, 3.5 to 31.2 pg ml⁻¹; IL-13, 32.0 to 62.5 pg ml⁻¹; TNFα, 1.6 to 15.6 pg ml⁻¹; and IL-10, 3.9 to 7.8 pg ml⁻¹.

Statistical analysis

The sample size was calculated from a previous pilot study ($n=5$ patients in each study group). A median difference of 28% in IL-6 concentrations was found in the pilot study for the two groups. For a type one (α) error level of 0.05 and a type II (β) error level of 0.2, we calculated a minimum required sample size of 20 patients per group. We estimated a maximum 15% loss, resulting in a minimum sample size of for each group. Data were tested for normality using the Kolmogorov Smirnov test. Preinduction concentrations were considered baseline. Concentrations recorded at each subsequent time interval were expressed as percentage of baseline concentration. To eliminate the influence of differences in preinduction concentrations of interleukins on calculation of area under the curve (AUC), between-group AUC comparisons of these percentages were performed using the Mann-Whitney U -test. Post hoc comparisons between repetitive measures of the same continuous variable were assessed using the Wilcoxon test. For these comparisons, Bonferroni adjustment was used, leading to an α reduction up to 0.01 threshold. Between-group single-measurement differences were assessed using the Mann-Whitney U test or Student's t -test according to the normality of data. Chi-square test was used to test correlations between qualitative data. The Mann-Whitney U -test was used to compare the incidence of PONV in the study groups.

On the basis of data distribution, continuous data were expressed as either mean (SD) or median (range). SPSS 17.0 (SPSS Inc., Chicago, IL) and Medcalc 8.3.1.1. (MedCalc Software, Mariakerke, Belgium) statistical packages were used to perform all data analyses.

Results

Of the 46 enrolled patients, 42 completed the study. One patient was excluded from the dexamethasone group because of acute inflammation of the gall bladder

Table 1 Demographic data of study groups

| | Dexamethasone (n = 22) | Control (n = 20) |
|-------------------------|---------------------------|---------------------|
| Age (years)* | 54.9 (13.5) | 50.8 (13.9) |
| Weight (kg)* | 75.5 (14.5) | 80.3 (7.6) |
| Sex (F/M) | 14/8 | 12/8 |
| ASA I/II | 10/12 | 10/10 |
| Anaesthesia time (min)* | 41.6 (10) | 44.9 (9.8) |

*Mean (SD).

discovered intraoperatively despite meeting the inclusion criteria, and three patients were excluded from the control group due to technical problems. We present the data from the remaining 42 patients who completed the study.

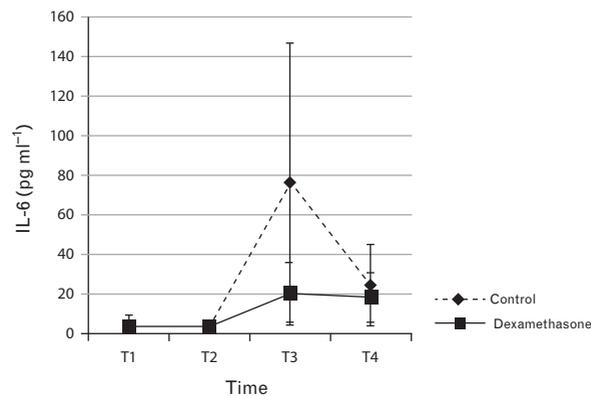
Demographic and clinical data were similar in both groups (Table 1). None of the patients became hypothermic during surgery; the mean intraoperative temperature was 36.5 (0.3)°C.

Preinduction plasma concentrations of all interleukins were within the normal ranges and did not differ between study groups for TNF α , IL-1 β , IL-6 or IL-8, although there were differences for IL-10 and IL-13.

AUCs for perioperative variation of IL-6 ($P = 0.0003$) and IL-8 ($P = 0.0001$) were significantly higher in the control group (Table 2). There were no significant differences in AUCs between study groups for IL-1 β , TNF α , IL-10 or IL-13. The time courses of plasma concentrations for IL-6, IL-8 and IL-10 are shown in Figs. 1–3. Immediately after induction, and before surgery, most of the interleukin concentrations were lower than baseline concentrations, especially in the dexamethasone group, wherein all values were lower. For IL-8 and IL-10, these differences were significant ($P = 0.002$ and 0.006 , respectively). In the control group, the concentrations of IL-8 and IL-10 were increased, but the differences were not significant ($P = 0.121$ and 0.60 , respectively). It can be seen from Figs. 1–3 that the greatest variations occurred 2 and 24 h postoperatively (T3 and T4) and we have analysed these data in detail.

Two hours postoperatively (T3), the concentrations of IL-6, IL-8 and IL-10 were significantly higher than baseline values in the control group, whereas in the

Fig. 1



Plasma interleukin-6 concentrations expressed as median (IQR). T1, before induction; T2, immediately after induction; T3, 2 h after skin closure; T4, 24 h after skin closure.

dexamethasone group, only IL-6 and IL-10 concentrations were significantly increased (Table 3). The greatest variations were in IL-6 and IL-8 in the control group and in IL-10 in the dexamethasone group.

Twenty-four hours postoperatively (T4), plasma concentrations of most of the interleukins returned close to the initial concentrations (Table 3). The concentration of IL-6 remained significantly higher than baseline in both groups after 24 h, with a higher median concentration in the control group than in the dexamethasone group. However, the difference was not statistically significant ($P = 0.9$).

Concentrations of IL-10 and IL-13 did not change significantly from the baseline values in either group (Table 3).

The concentrations of IL-8 were significantly lower in the dexamethasone group ($P = 0.006$) and did not change from baseline values in the control group ($P = 0.232$). The concentration of IL-13 did not differ between study groups at any time point and the concentrations were always within the normal range.

The data relating to PONV are summarised in Table 4. There were no significant differences in the total

Table 2 Results of longitudinal between-group comparisons

| | Dexamethasone | | Control | | P |
|--------------|---------------|-----------------|---------|------------------|---------|
| | AUC | 95% CI | AUC | 95% CI | |
| IL-6 | 1228.8 | 442.1 to 1675.0 | 3282.3 | 2065.1 to 5972.1 | 0.0003 |
| IL-8 | 215.5 | 135.1 to 329.8 | 405.7 | 348.7 to 511.1 | <0.0001 |
| IL-10 | 597.5 | 426.9 to 962.2 | 472.3 | 63.5 to 714.1 | 0.449 |
| IL-13 | 289.2 | 274.1 to 309.6 | 309.8 | 290.1 to 332.9 | 0.114 |
| IL-1 | 296.5 | 413.6 to 267.4 | 324.3 | 284.6 to 364.4 | 0.743 |
| TNF α | 278.4 | 258.1 to 306.3 | 301.9 | 275.5 to 316.5 | 0.404 |

Areas under the curve were calculated using baseline values as the common reference point for both groups. Between-group longitudinal comparisons were performed using Mann–Whitney U -test. AUC, area under the curve; CI, confidence interval; IL, interleukin; TNF, tumour necrosis factor.

Table 4 Incidence of postoperative nausea and vomiting and antiemetic medication in study groups

| | Dexamethasone (n = 22) | Control (n = 20) | P |
|---|------------------------|------------------|------|
| PONV (number of patients) | 9 | 8 | 0.96 |
| PONV (episodes/patient) | 0.50 (0.61) | 1.10 (1.92) | 0.85 |
| Metoclopramide consumption (mg kg ⁻¹ per 24 h) | 0.05 (0.06) | 0.05 (0.08) | 0.89 |

PONV, postoperative nausea and vomiting.

None of the patients was readmitted because of postoperative complications after discharge from hospital.

Discussion

Despite the fact that dexamethasone has been used for almost two decades as routine prophylaxis against PONV, especially after laparoscopic surgery,^{1,12} there are only a few reports about its adverse effects,^{4,16} focused mainly on clinical side effects: haemorrhage; wound infection; delayed wound healing; and increased glucose concentrations. Even less is known about the immunological effects of a single prophylactic dose of dexamethasone or about its effect on the inflammatory response. It has been demonstrated that the administration of corticosteroids in the preoperative period is followed by suppression of inflammation^{12,17} without an increased risk of postoperative infectious complications.¹⁸ However, there are studies showing that there are nonsurgical situations in which glucocorticoids may have pro-inflammatory effects.¹⁹

Interleukins are proteins that are partly responsible for the inflammatory response after surgery and anaesthesia.^{20–22} The overall inflammatory response results generally from the balance between pro-inflammatory and anti-inflammatory interleukins.²³ Abnormally increased concentrations of these interleukins can promote either an increased inflammatory process with subsequent deleterious effects on other organs such as multiple organ dysfunction,²⁴ or a decreased inflammatory response with a risk of infectious complications after surgery.^{25–27}

IL-13, produced by T-helper type 2 cells, mast cells and basophils, has been studied only recently in relation to anaesthesia and surgery and its role as a pro-inflammatory or anti-inflammatory or both is still controversial.²⁸ Initially considered a variant of IL-4, IL-13 has been described as involved in specific inflammatory processes as well as in tissue remodelling.²⁸

Our findings indicate that there were no significant differences produced by dexamethasone 4 mg in the concentrations of IL-1 β , TNF α or IL-13 evaluated as AUC of percentages from baseline values of the plasma concentrations for the first 24 h postoperatively. The AUC of plasma concentration variation of IL-6 and IL-8 were significantly higher in the control group, whereas for IL-10, differences were slightly greater in the dexamethasone group. Two hours postoperatively,

concentrations of IL-6 and IL-10 were significantly increased in both groups, while IL-8 was significantly increased in the control group. At 24 h, only IL-6 concentrations remained significantly increased in both groups, with a higher median value in the control group (although not statistically significant). IL-10 remained increased only in the control group, probably to counteract the abnormally increased concentration of IL-6.

Our findings are in agreement with previous studies showing that the greatest increase in plasma interleukins IL-6 and IL-10 occur in the first 2 to 4 h after surgery and diminish during the subsequent 24 h.^{29–32} In a study similar to ours, El Azab *et al.*²⁵ demonstrated that much higher doses of dexamethasone (100 mg) had an effect on IL-6, IL-8 and IL-10 similar to what we found using a dose of only 4 mg. Contrary to the findings of El Azab *et al.*,²⁵ the administration of dexamethasone did not influence the concentration of TNF α , probably because of the low dose of dexamethasone and less stimulating surgery.

Despite a long biological half-life (36 to 72 h),³³ dexamethasone influences cytokine concentrations during the perioperative period earlier than it influences PONV.⁴ Dexamethasone 4 mg decreased the concentrations of inflammatory cytokines immediately after induction of anaesthesia and during surgery, whereas 24 h postoperatively, the interleukin concentrations were returning towards their preoperative concentrations.

It is difficult to compare different studies of the effect of dexamethasone on cytokine balance during different surgical procedures because of different doses and study protocols.^{16,18} The influence of anaesthetic agents must also be taken into consideration. However, studies with different doses have shown similar effects: a shift of the cytokine balance towards anti-inflammatory interleukins and diminished concentrations of pro-inflammatory cytokines, which may be responsible for the favourable postoperative recovery of these patients.

Our study has a few limitations. First, due to a small sample size and the variability in cytokine concentrations in the pilot study, our study may be underpowered in respect of some of the interleukins in which differences between groups were not as great as for IL-6. We followed up the patients only for 24 h until discharged; a longer observation time may have detected a further decrease in IL-6 concentration. Our findings can only partly explain some of the beneficial effects reported with

dexamethasone.^{12,18} It would also be interesting to know whether such a low dose of dexamethasone has the same effect during inhalational anaesthesia or if the effects are dose-related. However, the small sample size may be responsible for the lack of difference in the incidence of PONV in the study groups or the use of neostigmine to antagonise residual muscle relaxation and pethidine for postoperative analgesia in the absence of NSAIDs.

A dose–response relationship study on the effects of dexamethasone on the inflammatory response would also be of interest, but such a study should take into consideration that the most commonly recommended doses of dexamethasone for PONV prophylaxis are of 4 to 5¹ and 8 mg, and only inconsistently other doses.^{5,34} Fujii and Itakura³⁵ reported differences in the incidence of PONV after laparoscopic cholecystectomy, with almost half as many patients suffering PONV after a dose of 8 mg compared with patients who had received 4 mg.

We do not have an explanation for the differences in preanaesthetic plasma concentrations of IL-10 and IL-13 between groups, although these concentrations were within the normal ranges and there were no differences in the other marker concentrations. This is why we have calculated differences in the change in interleukin concentration rather than the absolute values.

We did not design the study to identify specifically whether there was a correlation between interleukin concentrations and the incidence of PONV, but our data suggest that there is no such correlation.

In conclusion, our results indicate that a small prophylactic dose of dexamethasone significantly diminishes the postoperative increase in pro-inflammatory IL-6 and IL-8. Concentrations of TNF α , IL-1 β and IL-13 were not influenced by this dose of dexamethasone. The clinical relevance of these effects is unclear but seems unlikely to be significant, taking into consideration the amplitude of the effect. Such an effect on inflammatory interleukins might be important in patients with increased concentrations of interleukins, such as those with the systemic inflammatory response syndrome. Further studies on larger groups of patients are needed to evaluate the magnitude of this effect and its clinical implications.

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the article and final approval of the manuscript to be submitted. T.M. had a substantial contribution to analysis and interpretation of data, revising of article in draft and final approval of the manuscript to be submitted.

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Conflicts of interest: None declared.

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