

# The Effects of a Small Dose of Dexamethasone on Cell Adhesion Molecules during Laparoscopic Cholecystectomy

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## Abstract

**Background and Objective:** There are only a few publications on the effects of dexamethasone on the plasma levels of cell adhesion molecules (CAMs). The goal of this study was to investigate the effects of dexamethasone 4 mg on the perioperative plasma levels of CAMs (soluble intercellular adhesion molecules [sICAM-1] and soluble vascular cell adhesion molecules [sVCAM-1]) during laparoscopic cholecystectomy.

**Methods:** Forty-two patients undergoing laparoscopic cholecystectomy under total intravenous anesthesia were enrolled and randomly divided into two groups: the first group received dexamethasone 4 mg (DEX group, n = 21) and the second group were controls (C group, n = 21). Plasma levels of sICAM-1 and sVCAM-1 were assessed before anesthesia, after induction (before surgery), and at 2 and 24 hours after surgery, respectively. Comparisons were performed for area under the plasma concentration-time curve (AUC) and within-group values.

**Results:** AUC comparison for sICAM-1 showed significantly increased levels in the C group ( $p=0.036$ ), while there was no significant difference for sVCAM-1 ( $p=0.052$ ). Within-group analysis showed increased levels for both sICAM-1 and sVCAM-1 in the C group at 24 hours postoperatively ( $p=0.35$  and  $p=0.025$ , respectively).

**Conclusions:** In our study, dexamethasone 4 mg given before laparoscopic cholecystectomy determined a significant decrease in plasma levels of sICAM-1.

Both sICAM-1 and sVCAM-1 remained increased compared with baseline at 24 hours in the C group. This may partially explain the postoperative anti-inflammatory effects of dexamethasone. Further studies are needed.

## Introduction

Interactions between cells and different substratum are mediated through different families of receptors, among which cell adhesion molecules (CAMs) as a part of the immunoglobulin superfamily are included. Due to their implications in cell interactions, CAMs are involved in numerous processes such as wound healing,<sup>[1,2]</sup> and inflammatory responses such as atherosclerosis or ischemia-reperfusion lesions.<sup>[3]</sup>

Two of the most studied CAMs are intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs). ICAMs are present in low concentrations on the surface of leukocytes and endothelial cells; they are involved in stabilizing cell-cell interactions and in leukocyte transmigration through the endothelial wall. Recent studies have shown implications of ICAMs as viral entry molecules and in signal transduction.<sup>[4,5]</sup> VCAMs are expressed in blood vessels after endothelial cell stimulation by cytokines. VCAMs are also involved in signal transduction and in certain inflammatory diseases such as atherosclerosis and rheumatoid arthritis.<sup>[3]</sup>

There is limited information on the effects of anesthesia on CAMs<sup>[6]</sup> and even less is known about the effects of dexamethasone on these molecules. The information available refers to high doses of corticosteroids, which have been found to inhibit the release of ICAMs or the expression of VCAMs due to high levels of interleukins.<sup>[7,8]</sup>

Our study was designed to investigate the effects of a small dose of dexamethasone on CAMs. The primary outcome of this study was the evaluation of plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) in patients with and without prophylactic dexamethasone for postoperative nausea and vomiting (PONV) during laparoscopic cholecystectomy under total intravenous anesthesia (TIVA).

## Methods

Ethical approval was provided (No. 178C) by the Ethics Committee of the "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, (president Prof. Dr F. Loghin) on 19 December 2007.

After ethical approval and written informed consent, 46 patients (American Society of Anesthesiologists physical status scores I or II [ASA I and II]) undergoing laparoscopic cholecystectomy under TIVA were included in the study. Patients were randomly divided by a computer-generated randomization sequence into two study groups: the first group received dexamethasone 4 mg (DEX group, n=23) before induction of anesthesia and the second group were controls (C group, n=23). Patients with acute cholecystitis, other inflammatory diseases, immune disorders, obesity (body mass index  $\geq 30$ ), diabetes mellitus, allergies, gastric ulcers, asthma, history of PONV, or current use of steroid or anti-inflammatory medication were excluded from the study. Although there is no direct connection between CAMs and these criteria, taking into consideration that both ICAMs and VCAMs can be induced by tumor necrosis factor and interleukin-1- $\beta$ , we chose to exclude all conditions that might interfere with the levels of these cytokines.

Anesthetic protocol was the same in both groups. All patients were premedicated with oral midazolam 7.5 mg. After arriving in the operating room, an intravenous cannula was inserted, blood samples were drawn for preoperative CAMs assessment and crystalloid 500 mL infusion was started. A second intravenous cannula was inserted and used for anesthetic drug administration. TIVA was induced with target-controlled infusion – propofol at an initial plasma concentration of 4  $\mu\text{g}/\text{mL}$  (Orchestra<sup>®</sup> Base Primea, Fresenius Vial SAS, Brézins, France) and remifentanyl administered by manual controlled in-

fusion with 0.5 µg/kg/min in the first minute and 0.25 µg/kg/min thereafter.

Tracheal intubation was facilitated with atracurium 0.6 mg/kg. During maintenance of anesthesia propofol, plasma concentration was adjusted to maintain a Bispectral Index® (BIS®) [Spacelabs Healthcare, Issaquah, WA, USA] between 40 and 55, and remifentanil was adjusted in 0.05 µg/kg/min steps according to patient needs.

If necessary, additional atracurium 10 mg was administered. Propofol and remifentanil infusions were stopped after the last stitch and muscle paralysis antagonized with neostigmine 2.5 mg and atropine 1 mg.

Monitoring included measurement of mean arterial blood pressure at 4-minute intervals, heart rate, oxygen saturation, end-tidal carbon dioxide (CO<sub>2</sub>), peripheral temperature and BIS®. Respiratory rate and inspiratory pressure were adjusted to maintain an end-tidal CO<sub>2</sub> of 35–45 mmHg.

Hypotension (defined as a decrease of blood pressure with over 25% of baseline values) was corrected with an increased rate of fluid administration and/or boluses of intravenous ephedrine 5 mg.

The postoperative analgesia regimen included oral paracetamol 1 g/8 h and intravenous pethidine 0.4–0.5 mg/kg at patients' request or when pain score on a visual analog scale (VAS) was ≥3 (on a 5-point VAS scale, 5 = worst pain possible, 0 = no pain). PONV was treated when necessary with intravenous metoclopramide 10 mg; if metoclopramide was not efficient (nausea and vomiting after metoclopramide), ondansetron 4 mg was given.

Crystalloid 1000 mL and low-molecular-weight heparins were also included in the postoperative prescriptions. NSAIDs were avoided because of the interference with interleukins and CAMs levels.

#### Measurement of Cell Adhesion Molecules

Only sICAM-1 and sVCAM-1 were assessed in this study. Separate dedicated kits are available for soluble intercellular adhesion molecule-2 through to soluble intercellular adhesion molecule-5.

Blood samples for ICAM-1 and VCAM-1 measurement were collected at the following time intervals: (i) before induction, at arrival in the operating room (T1); (ii) before surgery, after

induction of anesthesia (T2); (iii) at 2 hours after surgery (T3); and (iv) at 24 hours after surgery (T4). Samples (7 mL) were drawn via an indwelling intravenous cannula inserted into a forearm vein, collected in Vacutainer® (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) tubes and centrifuged at 2500 rpm for 10 minutes at room temperature. Separated plasma samples (3–4 mL) were stored in cryotubes (Citotest® Labware Manufacturing Co, Ltd, China) below –30°C according to manufacturer indications until assay.

sICAM-1 and sVCAM-1 were measured using commercially available kits (Quantikine®, R&D Systems Inc., Minneapolis, MN, USA) and a two-step sandwich ELISA. In the first step standards and plasma samples were pipetted into the wells of ELISA plates where CAMs are bounded by previously coated immobilized specific antibodies. Detection antibodies were added after washing the plate. The final result of the reactions is a yellow product whose optical density is measured and is related to the amount of the molecule bound in the initial step. The sample values are then read from a standard curve.

Detection limits as given by the manufacturer are within the following ranges: sVCAM-1 0.17–1.26 (mean = 0.6) ng/mL; sICAM-1 0.049–0.254 (mean = 0.096) ng/mL, with intra- and interassay coefficients of variation both less than 8% (Quantikine®, R&D Systems Inc., Minneapolis, MN, USA).

Normal plasma values of CAMs as given by the manufacturer are within the following ranges: sVCAM-1 349–991 ng/mL; sICAM-1 98.8–320 ng/mL.

#### Statistical Analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 8.3.1.1. statistical packages. We calculated a sample size based on the results of a pilot study (n = 5) that showed a 28% median level difference between groups in pro-inflammatory cytokine (interleukin-6) levels. For a type I error (alpha level) of 0.05 and a type II error (beta level) of 0.20, we calculated a minimum required sample size of 20 patients per group. Due to a previous

**Table I.** Demographic data of the study groups

| Parameter                          | DEX group (n=21) | C group (n=21) | p-Value |
|------------------------------------|------------------|----------------|---------|
| Age (y) <sup>a</sup>               | 54.00±14.64      | 50.4±13.95     | 0.42    |
| Weight (kg) <sup>a</sup>           | 75.85±14.78      | 79±7.57        | 0.39    |
| Sex (F/M)                          | 12/9             | 13/8           | 0.5     |
| ASA I/II                           | 9/12             | 11/10          | 0.75    |
| Anesthesia time (min) <sup>a</sup> | 49.95±20.19      | 42.5±5.57      | 0.11    |
| IV fluids (mL) <sup>a</sup>        | 1214.28±253.54   | 1250±256.49    | 0.65    |

a Data are expressed as mean ± SD.

**ASA I/II**=American Society of Anesthesiologists physical status scores I or II; **C**=control; **DEX**=dexamethasone; **F**=female; **IV**=intravenous; **M**=male.

experience from the pilot study, we estimated a maximum loss of 15% of the enrolled patients and this resulted in a maximum sample size of 23 patients per group. Data were tested for normality using the Kolmogorov-Smirnov test. Longitudinal data were examined using summary measure analysis as described.<sup>[9]</sup> Comparisons of the area under the plasma concentration-time curve were performed between groups using the Mann-Whitney U test. The Wilcoxon signed-rank test was used to assess differences between repetitive measures of the same continuous variable. Single measurement differences between the groups were assessed using the Mann-Whitney U test or Student's t-test according to the normality of data. The chi-square test was used to test correlations between qualitative data. Continuous data were expressed as either mean plus or minus standard deviation or median (minimum–maximum) values, depending on normality of data. A p-value of <0.05 was considered statistically significant.

## Results

Study groups were similar with regard to demographic data (see table I). Altogether, 42 patients

completed the CAMs analysis during the first 24-hour postoperative period. Two patients were excluded from the DEX group due to an acute cholecystitis (diagnosed intraoperatively) and technical problems; two patients were excluded from the C group due to technical problems (one patient was discharged earlier than 24 hours postoperatively and one patient had missing samples).

None of the patients became hypothermic during surgery. Mean temperature during anesthesia was 36.5±0.288°C.

In both groups all pre-induction values of CAMs were within the normal ranges as given by the manufacturer. Pre-induction levels did not differ between study groups for both sICAM-1 or sVCAM-1 (see table II).

Area under the plasma concentration-time curve comparison between study groups revealed significant differences for sICAM-1 (p=0.036), with greater levels in the C group, and insignificantly greater levels for sVCAM-1 (p=0.052), in the DEX group (see table III).

From the plasma concentration-time curve of CAMs as shown in figures 1 and 2, it can be seen that the greatest variations were registered at T3 and T4. However, both sICAM-1 and sVCAM-1 variations showed less variability in the DEX group than in the C group. This is why we proceeded with a within-group analysis.

Within-group comparisons of plasma levels of CAMs at T3 and T4 are shown in tables IV and V, respectively.

No significant differences were registered at T3 in either sICAM-1 or sVCAM-1 plasma levels when compared with baseline values in both study groups (see table IV). However, at T4, the sVCAM-1 levels remained significantly higher than baseline in the C group (p=0.025), while sICAM-1 plasma levels were insignificantly increased in the C group also (p=0.35) [see table V].

**Table II.** Pre-induction plasma levels of cell adhesion molecules (CAMs) in study groups<sup>a</sup>

| CAM             | DEX group (n=21)     | C group (n=21)      | p-Value |
|-----------------|----------------------|---------------------|---------|
| sICAM-1 (pg/mL) | 62.29 (31.7–76.1)    | 69.23 (19.6–153.3)  | 0.062   |
| sVCAM-1 (pg/mL) | 302.20 (209.8–389.2) | 284.51 (68.0–329.3) | 0.070   |

a Data are expressed as median (minimum–maximum).

**C**=control; **DEX**=dexamethasone; **sICAM-1**=soluble intercellular adhesion molecule-1; **sVCAM-1**=soluble vascular cell adhesion molecule-1.

**Table III.** Results of between-group longitudinal comparisons of plasma levels of cell adhesion molecules (CAMs) in study groups

| CAM     | DEX group (n=21) |                 | C group (n=21)   |                | p-Value |
|---------|------------------|-----------------|------------------|----------------|---------|
|         | AUC <sup>a</sup> | 95% CI          | AUC <sup>a</sup> | 95% CI         |         |
| sICAM-1 | 187.35           | 151.29, 198.52  | 227.74           | 162.23, 324.62 | 0.036   |
| sVCAM-1 | 884.84           | 833.02, 1092.09 | 843.31           | 787.87, 918.17 | 0.052   |

a AUC was calculated having baseline as common reference for both groups. Between-group longitudinal comparisons were performed using the Mann-Whitney U test.

**AUC**=area under the plasma concentration-time curve; **C**=control; **DEX**=dexamethasone; **sICAM-1**=soluble intercellular adhesion molecule-1; **sVCAM-1**=soluble vascular cell adhesion molecule-1.

## Discussion

Despite the fact that dexamethasone is used as a routine prophylaxis for PONV, especially after laparoscopic surgery,<sup>[10,11]</sup> for many years only limited adverse effects were reported.<sup>[12,13]</sup> Most of these reports focused on clinical adverse effects such as infections, wound healing, surgical hemorrhage, or other effects due to corticosteroid use.<sup>[12]</sup> As well as a decreased incidence of PONV, there are also reports on other beneficial effects of dexamethasone such as a decreased degree of pain and swelling or a more rapid discharge.<sup>[14,15]</sup>

Little is known about cellular and molecular effects of small doses of dexamethasone (e.g. those doses used for PONV prophylaxis) or about the effects on immune response. It has been demonstrated that higher doses of dexamethasone decrease the inflammatory response after surgery, especially after cardiac surgery.<sup>[16]</sup> This effect is mediated by the increase in plasma levels of anti-inflammatory interleukins and the decrease in pro-inflammatory interleukins. Less is known about the effects of high-dose dexamethasone on CAMs (ICAMs, VCAMs).<sup>[7,8,17,18]</sup> The effects of a small dose of dexamethasone on CAMs have not been studied until now.

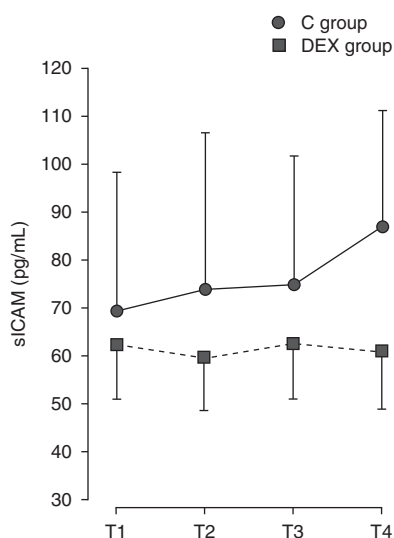
Apart from the effects of different CAMs on wound healing<sup>[1,2]</sup> or during the aforementioned inflammatory responses, such as atherosclerosis or ischemia-reperfusion lesions,<sup>[3]</sup> there are a few other important clinical effects related to inflammation or tumor progression. It has been shown that CAMs are involved in tumor progression and metastasis.<sup>[19-21]</sup> However, the implication of CAMs in these processes is evaluated differently in different studies. Some studies measure soluble forms<sup>[20]</sup> or expression of CAMs,<sup>[1,3]</sup>

while other studies evaluate CAMs as whole molecules.<sup>[1,19,21]</sup>

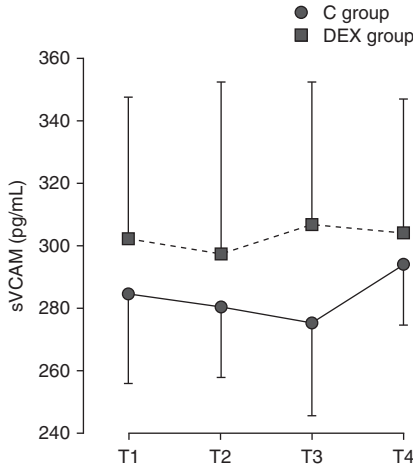
ICAMs and VCAMs are members of the immunoglobulin superfamily regulated by the inflammatory interleukins.<sup>[22]</sup>

ICAM-1 has five domains in its extracellular domain and soluble forms of mono- and dimeric ICAM-1 generated by proteolytic cleavage known as sICAM-1 were determined in our study. VCAMs also have extracellular domains and the soluble form that can be determined in plasma (sVCAM-1) also results from proteolytic cleavage.

The mechanisms involved in actions of CAMs are different for ICAM-1 and for VCAM-1.



**Fig. 1.** Plasma concentrations of soluble intercellular adhesion molecule (sICAM)-1 expressed as median (interquartile range). **C**=control; **DEX**=dexamethasone; **T1**=before induction; **T2**=immediately after induction; **T3**=at 2 hours after skin closure; **T4**=at 24 hours after skin closure.



**Fig. 2.** Plasma concentrations of soluble vascular cell adhesion molecule (sVCAM)-1 expressed as median (interquartile range). **C** = control; **DEX** = dexamethasone; **T1** = before induction; **T2** = immediately after induction; **T3** = at 2 hours after skin closure; **T4** = at 24 hours after skin closure.

ICAM-1 produces its effects by promoting recruitment and adhesion of leukocytes to the activated endothelium due to strong bonds with integrins, thus trapping the inflammatory cells to the vascular surface and promoting migration through endothelial cells.<sup>[23]</sup> On the other side, a decreased level of ICAM-1 may allow tumor cells to enter from the tissues into the vessel, thus promoting metastasis. VCAM-1 is produced mainly by the endothelial cells and other types of cells (i.e. smooth muscle cells) after being stimulated by the interleukins and it promotes adhesion of inflammatory cells to the vascular wall and subsequent migration.<sup>[20,24]</sup> Some of the tumor cells may also use VCAM-1 to adhere to the vascular wall and to migrate.<sup>[25-27]</sup>

CAMs are affected by surgery and, in turn, may influence outcome after oncologic surgery.<sup>[26-28]</sup> There are only a few studies on the effect of laparoscopic surgery on the level of CAMs. Laparoscopic surgery is well recognized as being able to reduce the amplitude of the inflammatory response,<sup>[29,30]</sup> so, theoretically, the levels of CAMs should also be reduced. However, when the levels of CAMs are the primary outcome parameter, the influence of CO<sub>2</sub> and the pressure of pneumoperitoneum must be taken into consideration as these may influence the levels of CAMs.<sup>[31,32]</sup> Attention must also be paid to the difference between plasma levels on one side and mucosal or peritoneal/mesenchymal levels of CAMs on the other side during laparoscopic surgery.<sup>[30,31]</sup>

Regarding the effects of dexamethasone on plasma levels of CAMs, the available data are conflicting. According to some studies, dexamethasone decreases the levels of CAMs,<sup>[17,33]</sup> while others have shown that dexamethasone does not influence the CAMs level or that dexamethasone only reduces the increased expression of CAMs due to an increased level of pro-inflammatory interleukins.<sup>[17,33-35]</sup> Most studies have focused on expression of ICAM-1 and VCAM-1; as the CAMs evaluation differs, it is difficult to compare different studies.

Our study showed that even a small dose of dexamethasone influenced the plasma levels of sICAM-1 and sVCAM-1. The difference is significant for sICAM-1 and did not reach statistical significance for sVCAM-1. Although there are not similar studies with such a low dose of dexamethasone used as prophylaxis for PONV during laparoscopic cholecystectomy, and the measured parameters are different (in our study, soluble

**Table IV.** Plasma levels of cell adhesion molecules (CAMs) in study groups: within-group comparison of values at 2 hours postoperatively with baseline values<sup>a</sup>

| CAM     | DEX group (n=21)    |                      | p-Value (DEX group) | C group (n=21)      |                      | p-Value (C group) |
|---------|---------------------|----------------------|---------------------|---------------------|----------------------|-------------------|
|         | T1                  | T3                   |                     | T1                  | T3                   |                   |
| sICAM-1 | 62.3 (31.7–76.1)    | 62.4 (29.3–75.9)     | 0.426               | 69.23 (19.66–153.3) | 74.75 (18.2–160.6)   | 0.911             |
| sVCAM-1 | 302.2 (209.8–389.2) | 306.77 (199.5–388.2) | 0.758               | 284.51 (68.0–329.3) | 275.33 (116.4–323.0) | 0.279             |

<sup>a</sup> Data are expressed as median (minimum–maximum).

**C** = control; **DEX** = dexamethasone; **sICAM-1** = soluble intercellular adhesion molecule-1; **sVCAM-1** = soluble vascular cell adhesion molecule-1; **T1** = before induction; **T3** = at 2 hours after skin closure.

**Table V.** Plasma levels of cell adhesion molecules (CAMs) in study groups: within-group comparison of values at 24 hours postoperatively with baseline values<sup>a</sup>

| CAM     | DEX group (n=21)    |                      | p-Value<br>(DEX group) | C group (n=21)      |                      | p-Value<br>(C group) |
|---------|---------------------|----------------------|------------------------|---------------------|----------------------|----------------------|
|         | T1                  | T4                   |                        | T1                  | T4                   |                      |
| sICAM-1 | 62.3 (31.7–76.1)    | 60.83 (28.0–75.2)    | 0.263                  | 69.23 (19.66–153.3) | 86.81 (12.1–160.6)   | 0.351                |
| sVCAM-1 | 302.2 (209.8–389.2) | 304.08 (209.8–388.0) | 0.986                  | 284.51 (68.0–329.3) | 294.05 (163.5–334.3) | 0.025                |

a Data are expressed as median (minimum–maximum).

C = control; DEX = dexamethasone; sICAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = soluble vascular cell adhesion molecule-1; T1 = before induction; T4 = at 24 hours after skin closure.

forms; in the others, expression of ICAM-1 and VCAM-1), our results are similar to those of Cronstein et al.<sup>[33]</sup> and Aziz and Wakefield,<sup>[34]</sup> showing that *in vitro* dexamethasone decreases the expression of CAMs induced by the inflammatory interleukins, and different from those of Dufour et al.,<sup>[35]</sup> who did not find an effect of dexamethasone on the level of CAMs. Regarding the increased levels of sICAM-1 and sVCAM-1 at 24 hours postoperatively, these may be at least partially determined by the increased postoperative levels of pro-inflammatory interleukins in the absence of dexamethasone described so far in the literature.

Our study had some limitations. First, the number of studied patients was small. With a larger number of patients, the results for CAMs might have been different. The sample size was calculated based on differences in interleukin-6 plasma levels in the pilot study, so our results may be underpowered with respect to sICAM-1 and sVCAM-1 levels.

We measured only soluble levels of ICAM-1 and VCAM-1; the effect of dexamethasone on expression of CAMs as transmembrane forms may be different. On the other side, we focused our study on plasma levels of CAMs; peritoneal levels may follow a different pattern.

## Conclusions

In conclusion, our study has shown that even a small dose of dexamethasone may decrease the level of sICAM, while the results for sVCAM did not reach statistical significance. Although CAMs are only part of the immune response, together with interleukins, they can at least par-

tially explain the beneficial anti-inflammatory effects of dexamethasone reported so far. The clinical relevance of these results is unclear and further studies on larger groups of patients are needed to further elucidate the effects of a small dose of dexamethasone on CAMs and their clinical significance.

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