

Dexamethasone for the Prevention of Postoperative Pain, Nausea, and Vomiting after Uncomplicated Laparoscopic Cholecystectomy. A Double-blind, Randomized Trial

Uso de Dexametasona para a Prevenção de Dor, Náusea e Vômitos Pós-Operatórios após Colectectomias Laparoscópicas Não-Complicadas. Um Estudo Duplo Cego e Randomizado

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ABSTRACT

The objective of this study was to investigate the effect of a single-dose of 8 mg of dexamethasone infused before induction of anesthesia to prevent pain, nausea, and vomiting after an uncomplicated laparoscopic cholecystectomy (LC). 70 non-consecutive patients who underwent uncomplicated LC were randomized to receive 8 mg of dexamethasone ($n = 37$) or saline ($n = 33$) intravenously 10-15 minutes before skin incision. Pain and nausea were measured on a visual analogue scale and the number of vomiting episodes after the surgery was registered. Dexamethasone did not change the perception of pain between the studied groups, but nausea sensation was relieved 1 hour ($p=0.0004$) and 6 hours ($p<0.01$) postoperatively. It diminished vomiting 1 hour after the reversion of anesthesia ($p=0.0007$), but this difference between the groups disappeared 6 and 24 hours after the reversion of anesthesia. In conclusion, 8 mg of intravenous dexamethasone decreased nausea and vomiting sensation after uncomplicated LC.

Key words: laparoscopy, glucocorticoids, anesthesia.

Bras. J. Video-Sur, 2011, v. 4, n. 2: 078-083

Accepted after revision: march, 18, 2011.

INTRODUCTION

Laparoscopic cholecystectomy (LC), a minimally invasive technique, is one of the most common elective surgical procedures in the western world. Compared to the conventional technique, it is associated with less surgical trauma and early return to activities of daily living.¹ Nevertheless, this technique is still associated with pain, nausea, and vomiting especially in the immediate postoperative setting, making the initial convalescence period unpleasant and uncomfortable.²

In the last few years, many drugs have been successfully used to prevent pain, nausea, and vomiting in the postoperative period.^{2,3} Glucocorticoids have known analgesic and anti-emetic effects and are widely used by anaesthesiologists for these purposes, and yet the effectiveness of glucocorticoids is still questioned. There are studies which do not recognize

the beneficial effects, and there are studies which demonstrate significant postoperative pain and nausea relief after preoperative dexamethasone infusion. Randomized clinical trials involving various major and minor surgical procedures have been conducted to examine the effects of preoperative administration of a single-dose of glucocorticoid on surgical outcome.⁴ However, research protocols as well as the analyzed outcomes have been heterogeneous, which contributed to the inconsistency of the observed results. In particular, the general anesthesia protocols for pain^{4,5} and nausea control are heterogeneous among the published observations. Because of this, the effectiveness of dexamethasone in the prevention of postoperative pain, nausea, and vomiting is unclear.

The purpose of this double-blind, placebo-controlled trial was to verify dexamethasone efficacy in the relief of pain, nausea, and vomiting in the first 24 hours after uncomplicated LC.

PATIENTS AND METHODS

This was a prospective, randomized, double-blind placebo-controlled trial in which 8 mg of intravenous dexamethasone was administered to the treatment group and saline was administered to the control group 10-15 minutes before skin incision. The observed outcomes were essentially clinical parameters.

Between March 2009 and September 2010, 70 patients who underwent laparoscopic cholecystectomy were observed. The exclusion criteria were: physical classification III of the American Society of Anaesthesiology (ASA); younger than 18 years old or older than 75 years old; a body mass index > 30; pregnancy; signs of endocrine, renal, hepatic, immunologic or cardiac diseases; opioid or tranquillizer intake within one week of the procedure; treatment with steroids; a history of alcohol or drug abuse; a preoperative diagnosis of vesicular empyema, or previous endoscopic sphincterotomy for biliary ducts or stones; and motion sickness. Patients who presented transoperative complications such as conversion to laparotomy, acute cholecystitis, pneumoperitoneum time exceeding 90 minutes, scleroatrophic gallbladder, patients with intraoperative biliary duct lesions, and elevated blood pressure variations during the procedure were also excluded from the analysis.

All the patients were properly informed about the study and affirmed their voluntary participation by signing the informed consent document, written with the parameters recommended by the Ethics Committee of the University of Pernambuco.

The patients who agreed to participate in the trial were instructed about the research and about the symptoms measurement mechanism. Then, they were randomly divided into two groups by a computer program. Each patient was codified by a single researcher who was aware of the randomization assignment. This researcher prepared the drug and administered the drug intravenously to the patient 10 to 15 minutes before the skin incision. Anesthesiologists, patients, and surgeons were blinded to the procedure and had no knowledge whether dexamethasone had been administered or not. The researcher verified that the intra- and postoperative anesthesia and analgesia protocol was strictly obeyed, that the patient's demographic data were documented, and

that the procedure was observed in order to ensure that the intraoperative exclusion criteria were followed.

The following drugs were administered to all the patients during general anesthesia: midazolam 5–15 mg, propofol 0.5–1.0 mg/kg, alfentanil 5-10 mg/kg, tracium 0.5 mg/kg, cefazoline 2 g, metoclopramide 10 mg, and inhaled sevoflurane. At the end of the procedure, prostigmine and atropine for neuromuscular paralysis reversion were administered. During anesthesia, the patient's cardiac rhythm and frequency, non-invasive blood pressure, pulse oxymetry, capnography, and intra-abdominal pressure were monitored.

A prophylactic and multimodal analgesic protocol was used for postoperative pain. Specifically, a total of 150 mg ropivacaine 0.75% was administered in all the trocar points before skin incision (50 mg in the 10-mm trocars and 25 mg in the 5-mm trocars), and ketoprofen (100 mg) was administered intravenously approximately 50 minutes before the end of the procedure. During the day of surgery, all the patients received dipirone 2 g intravenously every 8 hours. Additional ketoprofen was given when necessary. Additional doses of intravenous metoclopramide were administered for patients who presented with nausea with an intensity higher than 3 on the VAS.

The surgical approach consists in the establishment of a pneumoperitoneum which was created using an open technique. LC was performed using two 10 mm trocars and two 5 mm trocars, while maintaining a 12 mmHg intra-abdominal pressure. When necessary, an umbilical fascia incision was performed for gallbladder extraction. After the procedure, carbon dioxide was evacuated carefully from the abdomen. The nasogastric tube was removed from the patient before transfer to the ward. Throughout the 24-hour study, blood pressure, heart rate, and respiratory frequency were monitored every 6 hours, except during sleep.

After the surgery, a second researcher, absolutely blinded to the administered drug, assessed the patient's pain and nausea intensity according to the VAS presented to the patient before the surgery and registered the number of vomiting episodes (Figure 1). The data were stored using the patient's codification until the data analyses. The necessary information was obtained using standardized questionnaires, containing direct and easy to

comprehend questions that covered all the pre-established variables.

The pain and nausea grades and the number of postoperative vomiting episodes were quantified in the 1st, 6th, and 24th hours after the surgery. Pain and nausea were quantified using a VAS, and the associated pain and nausea intensity concepts (which range from absence of pain or nausea = 1, up to severe pain or nausea, non-responsive to medication = 5) as well as the number of postoperative emesis were computed. Pain was defined as a composite of incisional, visceral, and scapular pain. Nausea was defined as an imminent sensation of that one is about to vomit.

All the patients were discharged when their vital signs were stable and they could tolerate a light diet. Hospital stay was defined as the number of postoperative days (including the day of surgery) prior to discharge.

Data analyses. Data were expressed as mean values \pm standard deviation, median \pm range of distribution (min-max) or frequencies and percentages as appropriate. The Fisher exact test or χ^2 , Student's *t* (two-tailed unpaired), and Mann-Whitney *U*-test were used to analyze proportions, as well as parametric and nonparametric data, respectively. Postoperative 24-hour results were specifically analyzed for intergroup differences. A $p < 0.05$ was considered statistically significant.

Grade of Pain

- 1 - Absence of pain
- 2 - Tolerable pain with moments when patient does not remember it or with low intensity. In both cases, there is no need for medication.
- 3 - Pain with moments when the patient does not remember it, but there is a need for analgesic drugs.

4 - Unforgettable pain, need for analgesic drugs control symptoms.

5 - Persistent pain, even with use of analgesic drugs; there is no significant improvement.

Grade of Nausea

- 1 - Absence of nausea
- 2 - Tolerable nausea, with moments when the patient does not remember or of low intensity. In both cases, there is no need for medication. Nausea ceased with one episode of vomit.
- 3 - Nausea, with moments that are forgotten. Need for analgesic drugs.
- 4 - An unforgettable nausea. Need for anti-emetic drugs to control symptoms.
- 5 - Persistent nausea, even with the use of anti-emetic drugs; there is no significant improvement.

RESULTS

Thirty-three patients (47.2%) in the control group and 37 patients (52.8%) in the dexamethasone group were available for analysis. The groups were compared for age, gender, ASA score, skin color, and body mass index (BMI) (Table 1). All the patients were discharged 24 hours after the procedure. There was no need to extend the hospital stay in any of the cases for any reason. Complications such as fever, surgical incision infection, coleperitoneum, and intraoperative bleeding were not diagnosed in any of the patients.

Presence/absence of symptoms

8 mg of dexamethasone was administered intravenously 10-15 min before the skin incision decreased the number of patients who reported any degree of nausea and vomiting at 1 and 6 hours after



Figure 1 - A Visual analogue scale (VAS) used to measure pain and nausea.

Table 1 - Comparison of patients' demographics between the dexamethasone and control groups. ASA score: American Society of Anesthesiologists' classification; BMI: Body Mass Index.

	Dexamethasone group (n=37)	Control group (n=33)	P
Age (years)	40.6 ± 2.2	41.9 ± 2.9	NS
Gender (Female:Male)	30:7	31:2	NS
BMI	27.4 (19.7-47.4)	25.3 (19.1-46.5)	NS
Race (white/non-white)	14/23	11/22	NS
Married	24/13	14/19	NS
ASA score (1:2:3)	25:12:0	24:8:0	NS

surgery. There were no differences between the two groups with regard to the number of patients who reported any degree of postoperative pain (Table 2).

DISCUSSION

We demonstrated that when dexamethasone (8 mg) was administered intravenously 10-15 minutes before LC, postoperative nausea and vomiting were significantly reduced. No significant effects were observed in pain perception under the conditions of this clinical trial.

There are many reasons nausea and vomiting occurs after laparoscopic cholecystectomy: the use of anesthetic drugs, specifically opioids administered for the control of pain; the use of inhaled anesthetics; and the carbon dioxide utilized to induce and maintain

the pneumoperitoneum. Dexamethasone has long been employed for the prevention of nausea and vomiting and for postoperative pain relief. The effectiveness of dexamethasone, however, is still a matter of debate because of the conflicting results from well-designed clinical trials.^{5,6}

It is not possible, due to ethical reasons, to administer only intravenous dexamethasone for postoperative pain relief and nausea control or to fail to offer to the patient a safe and comfortable anesthesia in a clinical trial. For this reason, the clinical trials always include a safe anesthetic protocol and a postoperative protocol for pain and nausea management. This medical approach, which is ethically essential and justified, directly interferes with the perception of pain and nausea. As the trials employed different protocols that include drugs with

Table 2 - Number of patients who underwent LC who reported any degree of post-operative pain, nausea, or vomiting. Values in parentheses are percentages. Fisher exact test.

	Dexamethasone n=37 (52.9%)	Control n= 33 (47.2%)	P
Pain			
1 hour	30 (81%)	24 (72%)	NS
6 hours	26 (70%)	26 (78%)	NS
24 hours	17 (45%)	17 (51%)	NS
Nausea			
1 hour	6 (16%)	20 (60%)	0.0002
6 hours	3 (8%)	14 (42%)	0.0016
24 hours	2 (5%)	7 (21%)	NS
Vomits			
1 hour	1 (2.7%)	13 (39%)	0.0001
6 hours	1 (2.7%)	9 (27%)	0.004
24 hours	1 (2.7%)	4 (12%)	NS

diverse mechanisms of action, as well as various routes of administration and dosages, it is not surprising that the results obtained were not entirely in agreement.^{7,8,9,10} In the present work, we adopted a strict protocol for pain control that included opioids during surgery, local anesthetics at the points where trocars are introduced, and anti-inflammatory drugs. Postoperative opioid drugs were not prescribed so as not to increase nausea and vomiting. The adoption of this rigorous protocol for pain control may have hampered the recognition of the effect of dexamethasone in preventing postoperative pain. Under these clinical conditions, dexamethasone had no effect in preventing or decreasing postoperative pain, a finding this is consistent with the observations of others. Again, there are contradictory observations. Bisgaard and colleagues⁵ employing a rigorous protocol for pain control that included fentanyl or alfentanil during general anesthesia, local anesthetic in all port sites, intravenous ketorolac, paracetamol administered using suppositories, and oral ibuprofen for pain control, and concluded that dexamethasone administered 90 min before LC reduced postoperative pain.

Prevention of nausea and vomiting following LC remains a medical challenge. Nausea and vomiting, regularly observed following LC, increase a patient's postoperative discomfort and suffering. The effectiveness of the powerful 5-HT₃ receptor antagonist in the prevention of postoperative nausea and vomiting is disappointing.¹¹ Other antiemetic drugs such as droperidol have prohibitive side effects or, like metoclopramide, are relatively ineffective for the prevention of post LC nausea and vomiting.^{3,12} Dexamethasone has been reported to reduce the incidence of postoperative nausea and vomiting and this effect is probably better than its effect in relieving postoperative pain.^{13,14}

According to our observations, dexamethasone was effective for reducing the perception of nausea up

to 6 hours after the surgery and for decreasing the episodes of vomiting up to 1 hour after surgery. These results are in accordance with others and are supported by systematic reviews about this matter. However, it is obvious that preoperative dexamethasone alone is not enough to prevent postoperative nausea and vomiting.

Some evidence suggests that the biological effects of dexamethasone begin 1-2 hours after administration. However, we and others administered 8 mg of dexamethasone 10-15 min before skin incision and observed results concerning prevention of nausea and vomiting similar to the ones published by Feo and colleagues and others who administered dexamethasone 90 min before surgery.⁵ Presumably, the beneficial effects of dexamethasone in preventing postoperative nausea and vomiting are only realized when the patient has recovered from general anesthesia. Considering the time spent to induce general anesthesia, to securely operate the patient, and in recovering from the anesthesia, it is probable that dexamethasone had time to achieve a clinically acceptable effect. Thus we believe that it is not necessary to administer the dose of dexamethasone 90 minutes in advance, and we recommend the administration of 8 mg of dexamethasone a few minutes before the beginning of anesthesia.

In this work, we carefully applied criteria of exclusion. We included criteria for picking only healthy patients with uncomplicated gallstones subjected to straightforward and short (less one hour) LC. We concluded, under the conditions of this trial, that a single dose of 8 mg of dexamethasone administered 10-15 min before beginning LC can prevent and relieve postoperative nausea and vomiting. We believe that future trials should consider the most effective combinations of antiemetic drugs and their doses should provide an answer to the medical challenge of preventing and relieving postoperative nausea and vomiting.

RESUMO

O objetivo deste estudo foi investigar o efeito de uma dose simples de 8mg de dexametasona aplicada antes da indução anestésica para prevenir dor, náuseas e vômitos após uma colecistectomia laparoscópica (CL) não complicada. Setenta pacientes não-consecutivos que foram submetidos a uma colecistectomia laparoscópica não-complicada foram randomizados para receber 8mg de dexametasona (n=37) ou solução salina (n=33) intravenosa 10-15 minutos antes da incisão na pele. Dor e náusea foram mensurados numa escala análoga visual e o número de episódios de vômitos após a cirurgia foi registrado. A dexametasona não mudou a percepção da dor entre os grupos estudados. Houve alívio na sensação de náusea na primeira (p=0.0004) e sexta hora (p<0.01) pós-operatórias; além disso, episódios de vômitos diminuíram uma hora após a reversão da indução anestésica (p=0.00007) e as diferenças entre os grupos desapareceram 6 e 24 horas após a reversão da anestesia. Em conclusão, 8mg de dexametasona intravenosa diminuíram náusea e vômitos após CL não-complicadas.

Palavras-chave: laparoscopia, corticoids, anestesia.

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