J Hepatobiliary Pancreat Surg (2009) 16:367–371
DOI 10.1007/s00534-009-0079-5

ORIGINAL ARTICLE

Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy: a prospective randomized double-blind study

Yasuyuki Fukami · Masaki Terasaki · Yoshichika Okamoto · Kenji Sakaguchi · Toru Murata · Masayuki Ohkubo · Kazumi Nishimae

Received: 11 June 2008 / Accepted: 27 July 2008 / Published online: 31 March 2009

Abstract
Background/Purpose Dexamethasone has been reported to reduce postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy (LC). However, its effect on other surgical outcomes such as pain and fatigue have been unclear. The purpose of this clinical study was to evaluate the efficacy of preoperative dexamethasone in ameliorating postoperative symptoms after LC.
Methods In this prospective, double-blind, placebo-controlled study, 80 patients scheduled for LC were analyzed after randomization to intravenous dexamethasone (8 mg) or placebo. All patients underwent standardized procedures for general anesthesia and surgery, and were recommended to remain in hospital for 3 postoperative days. Episodes of PONV, and pain and fatigue scores on a visual analogue scale (VAS) were recorded. Analgesic and antiemetic requirements were also recorded.
Results There were no apparent side effects of the study drug. Seven patients (18%) in the dexamethasone group reported nausea, compared with 16 (40%) in the placebo group ($p = 0.026$). One patient (3%) in the dexamethasone group and 7 (18%) in the placebo group reported vomiting ($p = 0.025$). Dexamethasone significantly reduced the postoperative VAS pain score ($p = 0.030$) and VAS fatigue score ($p = 0.023$). The mean number of patients requiring diclofenac sodium 50 mg was 0.9 ± 1.3 in the dexamethasone group and 2.2 ± 2.5 in the placebo group ($p = 0.002$).
Conclusions The regimen we employed is safe and without apparent side effects. These results suggest that preoperative dexamethasone (8 mg) significantly reduces the incidence of PONV, pain, and fatigue after LC.

Keywords Laparoscopic cholecystectomy · Dexamethasone · PONV · Complications

Y. Fukami (✉) · M. Terasaki · Y. Okamoto · K. Sakaguchi · T. Murata · M. Ohkubo · K. Nishimae
Department of Surgery, Shizuoka Saiseikai General Hospital, Shizuoka 422-8527, Japan
e-mail: yasuyuki490225@yahoo.co.jp

Introduction

Laparoscopic cholecystectomy (LC) has been a gold standard surgical method for the treatment of cholelithiasis, and also for some cases of cholecystitis and cholecystic polyp. Although the operative procedure of LC has been perfected and the surgical outcome is satisfactory, postoperative nausea and vomiting (PONV) are distressing side-effects, and high incidences have been reported (35–63%) [1, 2].

Glucocorticoids are well known for their antiemetic, analgesic, and anti-inflammatory effects. Dexamethasone has been used as an antiemetic drug for more than 25 years in patients receiving chemotherapy, with limited side effects [3, 4]. Numerous antiemetics have been applied for the prevention and treatment of PONV in patients after LC, and recently, several prospective studies have shown that dexamethasone reduces the severity of PONV after LC [2, 5–8].

On the other hand, the value of dexamethasone for other postsurgical symptoms such as pain and fatigue has been controversial and not fully assessed [2, 5, 6, 9]. In 26–41% of patients after LC, pain is the main reason for prolongation of the hospital stay overnight on the day of surgery, and is the predominant complaint and primary reason for prolonged convalescence [10–12].

If these complications could be ameliorated, patients could be discharged earlier and thus costs would be reduced. We thought that the simple and inexpensive use of preoperative dexamethasone at a low dose would deliver a benefit to patients after LC. Here we report a prospective, double-blind, placebo-controlled study to evaluate the efficacy of preoperative dexamethasone for the amelioration of nausea, vomiting, pain, and fatigue after LC.

Patients and methods

Patients

Between January 2006 and May 2008, 88 of 98 patients undergoing LC were studied in accordance with a prospective, randomized, double-blind, placebo-controlled protocol. Patients were randomized to intravenous dexamethasone (8 mg) or placebo saline 90 min before skin incision, using an equal number of blind envelopes. The hospital ethics committee approved the study, and all 88 patients gave signed informed consent before participating. Patients of American Society of Anesthesiologists (ASA) class IV were excluded. Further exclusion criteria were age more than 80 years; pregnancy; treatment with steroids; severe diabetes mellitus (HbA1c $> 8.5\%$); use of opioids or tranquilizers less than 1 week before LC; a history of alcohol or drug abuse; preoperative diagnosis of gallbladder carcinoma; acute pancreatitis; emergency operation; and conversion from LC to an open procedure (Fig. 1).

All patients were followed from the day before surgery and were recommended to remain in hospital for 3 days after surgery. Results for a final total of 80 patients were analyzed.

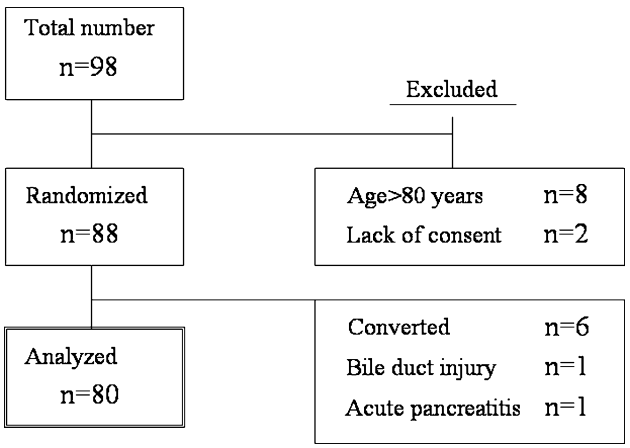

Fig. 1 Study flow chart

Anesthesia and surgery

All patients underwent a standardized general anesthesia procedure using fentanyl and propofol. Anesthesia was maintained with 1.0–2.5% sevoflurane in oxygen, and nitrous oxide in 50% oxygen. Neuromuscular block was maintained with vecuronium i.v. A nasogastric tube was placed during the operation in all patients.

All patients received preoperative intravenous antibiotics (second-generation cephalosporin). LC was performed using a two-handed, four-trocar technique with two 12-mm ports and two 5-mm ports. A 12-mm subumbilical port was introduced by the open method, subsequently creating a pneumoperitoneum, maintained at 8 mmHg intraabdominal pressure. In order to avoid contamination, the gallbladder was removed in an endoscopic bag. All of the laparoscopic treatments were performed by six surgeons, each having sufficient experience of laparoscopic surgery (more than 30 cholecystectomies). The skin was closed with single absorbable sutures. Closed suction drains were placed in the inferior surface of the liver, using a 5-mm lateral port. In all patients, the drains were removed on the morning after the operation.

Analgesia and antiemetics

Pain and fatigue were assessed preoperatively and at 0 (immediately on return to the recovery room), 6, 24, 48, and 72 h after the operation, in terms of a visual analogue scale (VAS; 0 = no pain/fatigue to 10 = most severe pain/fatigue) [5, 13]. Analgesics were given as a suppository (diclofenac sodium 50 mg) as needed. The incidence of nausea or vomiting was recorded preoperatively and at 0 (immediately on return to the recovery room), 6, 24, 48, and 72 h after the operation, using a four-point ordinal scale (0 = none, 1 = nausea, 2 = nausea with request for antiemetics, 3 = vomiting). Intravenous metoclopramide (10 mg) was given for antiemetic treatment on demand.

Data collection and statistical analysis

Postoperative complications were recorded during hospitalization, and the patients were followed up at least once after discharge. Data collected also included patient age, sex, body mass index (BMI), C-reactive protein (CRP) level, ASA score, history of previous abdominal surgery, anesthesia and operation time, and frequency of use of analgesics and antiemetics. These parameters were summed and compared between the dexamethasone and placebo groups.

The study endpoints were degree of postoperative nausea, vomiting, pain, and fatigue, and analgesic and antiemetic medication requirements.

The sample size was predetermined. We expected a 30% difference in the incidence of nausea and vomiting between groups. The α error was set at 0.05 and β error at 0.10; according to power analysis, a size of 37 patients for each group was considered adequate. We decided to enroll 40 patients per group. Results were expressed as means ± SD or numbers (percentages). Student's t test, the χ^2 test, and the Mann–Whitney U test were used for the analysis of parametric and non-parametric data. Differences at $p < 0.05$ were considered statistically significant.

Results

Eighteen patients were excluded from the study, because of age more than 80 years ($n = 8$), lack of consent ($n = 2$), bile duct injury ($n = 1$), acute pancreatitis ($n = 1$) and conversion from LC to an open procedure ($n = 6$; 6%). A total of 80 LC patients were enrolled (Fig. 1), 40 being randomized to intravenous dexamethasone (8 mg) and 40 to placebo. All patients stayed in the hospital for 3 days. There were no significant differences between the two groups with regard to mean age, gender, BMI, preoperative CRP level, ASA score, or anesthesia and operation times (Tables 1, 2).

Seven patients (18%) in the dexamethasone group reported nausea, compared with 16 (40%) in the placebo group ($p = 0.026$). One patient (3%) in the dexamethasone group and 7 (18%) in the placebo group reported vomiting ($p = 0.025$). The mean number of metoclopramide requirements was 0.2 ± 0.5 in the dexamethasone group and 0.5 ± 0.8 in the placebo group ($p = 0.032$; Table 3).

Dexamethasone significantly reduced postoperative pain just after surgery (VAS score, 5.6 ± 2.6 vs. 6.6 ± 2.2; $p = 0.030$) and at 6 h after the operation (VAS score, 3.3 ± 1.9 vs. 4.4 ± 2.4; $p = 0.021$; Table 4). During hospitalization, 19 patients (48%) in the dexamethasone group required a diclofenac sodium 50-mg suppository, compared with 32 (80%) in the placebo group ($p = 0.005$). The mean number of diclofenac sodium 50 mg requirements was 0.9 ± 1.3 in the dexamethasone group and 2.2 ± 2.5 in the placebo group ($p = 0.002$; Table 5). Dexamethasone significantly reduced postoperative fatigue just after the operation (VAS score, 3.6 ± 3.1 vs. 4.9 ± 2.6; $p = 0.023$), and at 24 h after the operation (VAS score, 1.4 ± 2.1 vs. 2.2 ± 2.0; $p = 0.032$) and 48 h after the operation (VAS score, 0.4 ± 0.9 vs. 1.2 ± 1.8; $p = 0.006$; Table 6).

There were no apparent side effects of the study drug, nor were there any cases of postoperative wound infection or bowel obstruction.

Table 1 Patient characteristics

	Dexamethasone ($n = 40$)	Placebo ($n = 40$)	p
Age (year)[a]	58 ± 15	56 ± 14	0.270
Sex ratio (M:F)	23:17	25:15	0.648
Body mass index (kg/m^2)[a]	24.4 ± 4.5	24.7 ± 3.4	0.370
CRP score (mg/dl)[a]	0.6 ± 1.2	0.4 ± 0.6	0.146
ASA score (I:II:III)	37:2:1	35:4:1	0.235
Previous abdominal surgery	12 (30%)	12 (30%)	NS

[a] Data are given as mean ± SD

Table 2 Operative data

	Dexamethasone ($n = 40$)	Placebo ($n = 40$)	p
Duration of anesthesia (min)[a]	130 ± 36	130 ± 41	0.500
Duration of surgery (min)[a]	73 ± 34	75 ± 36	0.401
Fentanyl (mg)	0.1	0.1	NS
Propofol (mg)[a]	87 ± 21	82 ± 15	0.117
Cholecystitis (no)	7/40	11/40	0.284

[a] Data are given as mean ± SD

Table 3 Postoperative nausea and vomiting

	Dexamethasone ($n = 40$)	Placebo ($n = 40$)	p
Nausea (no)	7 (18%)	16 (40%)	0.026
Vomiting (no)	1 (3%)	7 (18%)	0.025
Metoclopramide requirements[a]	0.2 ± 0.5	0.5 ± 0.8	0.032

[a] Data are given as mean ± SD

Table 4 Postoperative VAS pain score

Time after operation (h)	Dexamethasone ($n = 40$)	Placebo ($n = 40$)	p
0[a]	5.6 ± 2.6	6.6 ± 2.2	0.030
6[a]	3.3 ± 1.9	4.4 ± 2.4	0.021
24[a]	1.8 ± 1.4	2.4 ± 1.9	0.060
48[a]	0.9 ± 1.0	1.0 ± 1.4	0.401
72[a]	0.5 ± 0.9	0.7 ± 1.2	0.201

[a] Data are given as mean ± SD

Table 5 Analgesia (diclofenac sodium 50 mg) requirements

	Dexamethasone ($n = 40$)	Placebo ($n = 40$)	p
Patients (no)	19 (48%)	32 (80%)	0.005
Diclofenac sodium requirements[a]	0.9 ± 1.3	2.2 ± 2.5	0.002

[a] Data are given as mean ± SD

Table 6 Postoperative VAS fatigue score

Time after operation (h)	Dexamethasone ($n = 40$)	Placebo ($n = 40$)	p
0[a]	3.6 ± 3.1	4.9 ± 2.6	0.023
6[a]	2.7 ± 2.5	3.5 ± 2.7	0.072
24[a]	1.4 ± 2.1	2.2 ± 2.0	0.032
48[a]	0.4 ± 0.9	1.2 ± 1.8	0.006
72[a]	0.6 ± 1.1	0.8 ± 1.3	0.239

[a] Data are given as mean ± SD

Discussion

In this randomized, double-blind, placebo-controlled study, preoperative dexamethasone (8 mg) significantly reduced the incidence of PONV, pain, and fatigue after LC.

PONV is an unpleasant, distressing, and exhausting complication for patients. These effects may prolong recovery time, delay patient discharge, and increase hospital costs [8]. The etiology of PONV after LC is not entirely clear. Risk factors such as the intraoperative use of isoflurane and fentanyl [14, 15], nitrous oxide [16], carbon dioxide insufflation [17], stretching of the peritoneum and increased blood pressure in the peritoneal cavity [18], and postoperative administration of opioids [19] may contribute to these episodes. LC is a procedure that is usually well tolerated by the patient. However, high incidences of PONV after LC have been reported (35–63%) [1, 2]. In our study, the incidence of PONV in the placebo group was 40%, compared with 18% in the dexamethasone group.

Dexamethasone was first reported to be an effective antiemetic agent in patients receiving cancer chemotherapy in 1981 [3]. Since then, dexamethasone alone or in combination with other antiemetic drugs has also been reported to be effective for the prevention of nausea and vomiting after LC [1, 2, 5–9, 18, 20]. The mechanism of the antiemetic action of dexamethasone is not known. However, some reports have suggested central inhibition of prostaglandin synthesis, inhibition of endogenous opioid release, and changes in the permeability of the blood-brain barrier to serum proteins [21, 22].

The biological action of a glucocorticoid begins 1–2 h after administration [20]. Therefore, in this study, dexamethasone was administered 90 min before skin incision. The recommended dose of preoperative intravenous dexamethasone has been 8 mg in many randomized trials or meta-analyses [1, 9, 20].

The analgesic effects of glucocorticoids are mainly provided through the peripheral inhibition of phospholipase enzyme, thereby decreasing the products of the cyclooxygenase and lipoxygenase pathways in the inflammatory response [23, 24]. In the present study, dexamethasone significantly reduced both immediate postoperative pain and analgesic requirements in comparison with the placebo group. Although some previous studies have obtained similar results [5], others using intravenous dexamethasone have failed to show any analgesic benefits after LC [2, 6, 9]. In those studies, however, prophylactic multimodal analgesia was administered along with dexamethasone, and therefore the effect of dexamethasone on postoperative pain may have been masked. Holte and Kehlet [21] analyzed several randomized trials of procedures ranging from minor to major surgery involving perioperative single-dose glucocorticoid administration. They concluded that the administration of a single dose of glucocorticoid reduced postoperative pain after minor laparoscopic procedures and orofacial surgery [21].

Dexamethasone has been reported to decrease postoperative fatigue through its strong anti-inflammatory effect. It has been suggested that early postoperative fatigue after LC may be related to sleep disturbance and the inflammatory response during the first 2-3 postoperative days [5, 12]. Hence, in the present study, all patients were treated in accordance with a strictly standardized design and followed from the time of hospitalization for 3 postoperative days. Our results indicated that dexamethasone significantly reduced postoperative fatigue just after surgery, and at 24 and 48 h after surgery.

Long-term administration of glucocorticoids is associated with side effects such as an increased risk of infection, impaired wound healing, and other complications. However, in the present study, no apparent side effects associated with the single dose of dexamethasone were found. Of course, this individual trial was small, with statistically insufficient power to assess side effects. However, these results were similar to those obtained in other randomized trials and meta-analyses [1, 2, 5–7, 9, 18, 20, 21]. Therefore, the evidence supports the safety of a single preoperative dose of dexamethasone (8 mg) in healthy patients undergoing LC.

In conclusion, our results suggest that preoperative dexamethasone (8 mg) ameliorates nausea, vomiting, pain, and fatigue after elective LC, without apparent side effects, and it may be a valuable treatment in this respect.

References

1. Henzi I, Walder B, Tramer M. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg. 2000;90:186–94.
2. Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth. 1999;83:772–5.
3. Aapro MS, Alberts DS. Dexamethasone as an antiemetic in patients treated with cisplatin. N Engl J Med. 1981;305:520.
4. The Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. N Engl J Med. 1995;332:1–5.
5. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. Ann Surg. 2003;238:651–60.
6. Feo CV, Sortini D, Ragazzi R, De Palma M, Libomi A. Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. Br J Surg. 2006;93:295–9.
7. Nesek-Adam V, Grizelj-Stojcic E, Rasic Z, Cala Z, Mrsic V, Smiljanic A. Comparison of dexamethasone, metoclopramide, and their combination in the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Surg Endosc. 2007;21:607–12.
8. Wang JJ, Ho ST, Uen YH, Lin MT, Chen KT, Huang JC, et al. Small-dose dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Anesth Analg. 2002;95:229–32.
9. Elhakim M, Nafie M, Mahmoud K, Atef A. Dexamethasone 8 mg in combination with ondansetron 4 mg appears to be the optimal dose for the prevention of nausea and vomiting after laparoscopic cholecystectomy. Can J Anesth. 2002;49:922–6.
10. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain. 2001;90:261–9.
11. Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. Anesthesiology. 2006;104:835–46.
12. Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. Eur J Surg. 2001;167:84–96.
13. Christensen T, Stage JG, Galbo H, Christensen NJ, Kehlet H. Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. Surgery. 1989;105:46–50.
14. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. Anesthesiology. 1992;77:162–84.
15. Cohen MM, Duncan PG, Deboer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. Anesth Analg. 1994;78:7–16.
16. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003;97:62–71.
17. Fredman B, Jedeikin R, Olsfanger D, Flor P, Gruzman A. Residual pneumoperitoneum: a cause of postoperative pain after laparoscopic cholecystectomy. Anesth Analg. 1994;79:152–4.
18. Leksowski K, Peryga P, Szyca R. Ondansetron, metoclopramide, dexamethasone, and their combinations compared for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a prospective randomized study. Surg Endosc. 2006;20:878–82.
19. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350:2441–51.
20. Lee Y, Lai HY, Lin PC, Lin YS, Huang SJ, Shyr MH. A dose ranging study of dexamethasone for preventing patient-controlled analgesia-related nausea and vomiting; a comparison of droperidol with saline. Anesth Analg. 2004;98:1066–71.
21. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg. 2000;195:694–712.
22. Livera P, Trojano M, Simone IL, Zimatore GB, Logroscino GC, Pisicchio L, et al. Acute changes in blood CSF barrier permselectivity to serum protein after intrathecal methotrexate and CNS irradiation. J Neurol. 1985;231:336–9.
23. Callery MP. Preoperative steroids for laparoscopic surgery. Ann Surg. 2003;238:661–2.
24. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21:55–89.