

Dexamethasone in Combination with Dolasetron for Prophylaxis in the Ambulatory Setting

Effect on Outcome after Laparoscopic Cholecystectomy

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Background: Postoperative nausea and vomiting after laparoscopic cholecystectomy remains a common problem despite routine antiemetic prophylaxis. Therefore, the authors investigated the effect of administering 4 mg intravenous dexamethasone as an adjunct to a 5-HT₃ antagonist (12.5 mg intravenous dolasetron) with respect to patient outcome.

Methods: Outpatients (N = 140) were enrolled in this prospective, randomized, placebo-controlled, double-blind, institutional review board-approved protocol involving two antiemetic treatment groups. After induction of anesthesia, the control group received 1 ml intravenous saline, whereas the dexamethasone group received 4 mg intravenous dexamethasone. Both groups received 12.5 mg intravenous dolasetron at the time of gallbladder removal. A blinded observer recorded the recovery times, emetic episodes, rescue antiemetics, maximum nausea score, and time to achieve discharge criteria. Post-discharge side effects, as well as patient satisfaction and quality of recovery scores were assessed at 24 h after surgery.

Results: Although there was no difference in the incidence of postoperative nausea and vomiting in the early recovery period, the dexamethasone group had a shorter stay in the day-surgery unit (136 ± 57 vs. 179 ± 62 min) and more rapidly achieved discharge criteria (161 ± 32 vs. 209 ± 39 min). In addition, fewer patients in the dexamethasone group experienced nausea at home within 24 h after discharge (13 vs. 28%, *P* < 0.05). Finally, the dexamethasone group reported higher quality of recovery and patient satisfaction scores (*P* < 0.05).

Conclusions: The authors conclude that the adjunctive use of 4 mg intravenous dexamethasone shortened the time to achieve discharge criteria and improved the quality of recovery and patient satisfaction scores after laparoscopic cholecystectomy procedures in outpatients receiving prophylaxis with 12.5 mg intravenous dolasetron.

DESPITE antiemetic prophylaxis, the incidence of postoperative nausea and vomiting (PONV) remains unacceptably high after laparoscopic cholecystectomy procedures.¹ Recent studies suggest that the addition of dexamethasone, as part of a multimodal approach, can decrease PONV in high-risk patient populations.²⁻⁴ Stud-

ies involving ondansetron⁴⁻⁷ and granisetron^{2,3} have reported that the addition of dexamethasone can reduce PONV symptoms compared with the use of a 5-HT₃ antagonist alone. However, these studies have not demonstrated a significant benefit with respect to meaningful patient outcome measures.⁸

In a recent study, Zarate *et al.*⁹ reported that dolasetron, another 5-HT₃ antagonist, was more cost-effective than ondansetron for prophylaxis against PONV after otolaryngologic surgery. Dolasetron has been used for both the prophylaxis and treatment of PONV in high-risk outpatient surgical populations.⁹⁻¹¹ However, it has not been studied in combination with dexamethasone, a potent corticosteroid with postoperative antiinflammatory and antiemetic effects.¹²⁻¹⁴ A recent study found that dexamethasone appeared to have beneficial effects in facilitating earlier discharge independent of its antiemetic activity.¹⁵

We therefore designed a prospective study to evaluate the effect of dexamethasone in combination with dolasetron on the incidence of PONV, requirement for rescue antiemetic drugs, and time to discharge after laparoscopic cholecystectomy. We hypothesized that the addition of dexamethasone would improve the recovery profile and patient satisfaction.

Materials and Methods

After obtaining approval from the local institutional review board (University of Texas Southwestern Medical Center, Dallas, TX) and written informed consent, 140 outpatients, American Society of Anesthesiologists physical status I and II, who were undergoing laparoscopic cholecystectomy procedures were studied according to a prospective, randomized, double-blind, placebo-controlled protocol. Patients were excluded if they had received a prophylactic antiemetic within 24 h of surgery, had preexisting abnormalities involving any major organ system, had a history of drug abuse, were pregnant, were more than 50% greater than their ideal body weight, or were allergic to the study drugs. Patients were randomly assigned to either the control or dexamethasone group, and the study medication (saline or 4 mg dexamethasone) was prepared and administered by an investigator not involved in the patient's care or data collection. The patient, anesthesiologist, and observer were all blinded with respect to the study group.

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Received from the Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. Submitted for publication May 25, 2001. Accepted for publication September 19, 2001. Funded by a grant from Abbott Laboratories, Chicago, Illinois. Presented at the 16th Annual Meeting of the Society for Ambulatory Anesthesia, Indian Wells, California, May 3-6, 2001.

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No premedication was administered before entering the operating room. On arrival in the operating room, standard monitors were applied. After obtaining baseline vital signs, 2 mg intravenous midazolam was administered. Anesthesia was subsequently induced with 2 mg/kg intravenous propofol and 1 μ g/kg intravenous fentanyl. Maintenance of anesthesia consisted of sevoflurane (1–2% end tidal) in combination with 65% nitrous oxide in oxygen. After tracheal intubation, the control group received 1 ml saline and the dexamethasone group received 4 mg (1 ml) intravenous dexamethasone from identical-appearing syringes according to a computer-generated randomization sequence. All patients were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 32–36 mm Hg. When the gallbladder was removed, 12.5 mg intravenous dolasetron was administered to all patients. At the end of surgery, 60 μ g/kg intravenous neostigmine (5 mg maximum dose) and 12 μ g/kg intravenous glycopyrrolate (1 mg maximum dose) were administered for reversal of residual neuromuscular blockade. Before skin closure, the surgeon injected a mixture of 1% lidocaine and 0.25% bupivacaine at the fascial level of each surgical portal. In addition, all patients also received 30 mg intravenous ketorolac for preventive analgesia. The maintenance anesthetic was discontinued when the laparoscope was withdrawn from the abdominal cavity, and the nitrous oxide was discontinued after the last skin suture was placed.

Demographic data were obtained, including gender, weight, age, and history of PONV, motion sickness or smoking. The duration of surgery (from incision to application of the bandage) and anesthesia (from induction to discontinuation of the inhaled anesthetic) was also recorded. Recovery times were determined at 1-min intervals after discontinuation of the maintenance anesthetic by a blinded observer, including the time to awakening (*i.e.*, opening eyes in response to a verbal command) and orientation to person and place, as well as the time to achieve a modified Aldrete score of 10 and a fast-track score of 12 or higher.^{16,17} In addition, the total intraoperative dosages of propofol and fentanyl, the volume of intravenous fluids administered during surgery, duration of stay in the step-down (phase II) recovery area and postanesthesia care unit, as well as time to achieve discharge criteria and actual hospital discharge were recorded.

The incidence of PONV was assessed at 15-min intervals in the postanesthesia care unit and subsequently at 30-min intervals until discharge by an investigator (M. C.) who was blinded to the study medication. An emetic episode was defined as vomiting or retching occurring in a 2-min period.⁷ The criteria for administering a rescue antiemetic was either a repeated or prolonged emetic episode (lasting > 5 min) or a request by the patient for treatment of their emetic symptoms. Promethazine

(6.25 mg administered intravenously) was administered as the initial rescue antiemetic. If this first dose was ineffective, the same dose was repeated to a maximum of 25 mg administered intravenously. A second rescue antiemetic drug (0.625 mg intravenous droperidol) was administered only when the symptoms of PONV persisted after the maximum dose of promethazine administered. In the postanesthesia care unit, 25 μ g intravenous fentanyl was administered at 3–5-min intervals as needed for acute pain relief. The time to receive the first rescue antiemetic and analgesic medication and the total doses were also recorded.

Fitness for discharge was assessed at 15-min intervals and required that the patient be awake and alert, with stable vital signs on standing, able to walk without assistance, and be free of postoperative side effects. Hydrocodone (5 mg) with 500 mg oral acetaminophen was prescribed at the time of discharge. A follow-up telephone call was made to all patients 24 h after surgery to determine the incidence of PONV after discharge and to assess their quality of recovery (QoR) and the patient's satisfaction with the management of their PONV symptoms (using 100-point verbal rating scales, where 0 = poor and 100 = excellent).

Statistical Analysis

An *a priori* power analysis based on previous studies involving a similar ambulatory surgical population^{2,7} suggested that a group size of 67 would be adequate to determine a 40% difference in the incidence of PONV given an estimated baseline incidence of PONV in the control group of 50% (power = 0.80, α = 0.05). Data were analyzed using the Number Cruncher Statistical System (version 6.0; NCSS, Kaysville, UT) using the student *t* test for continuous variables and chi-square test for categorical data. $P < 0.05$ was considered statistically significant, and data were expressed as mean values \pm SD or number and percentages.

Results

There were no significant differences between the two treatment groups with respect to demographic data, duration of surgery and anesthesia, and history of motion sickness, PONV, or smoking (table 1). The doses of anesthetic drugs, including propofol, fentanyl, and volume of perioperative intravenous fluid did not differ between the two groups. Similarly, there were no significant differences in recovery times to awakening, orientation, achievement of fast-track score of 12, Aldrete's score of 10, or initiating oral intake (table 2). Furthermore, the postoperative opioid analgesic requirement, the time to receive the first analgesic and antiemetic rescue, was also comparable for the two groups.

Despite the lack of difference in both the incidence of

Table 1. Patient Characteristics, Duration of Anesthesia and Surgery, Intraoperative Anesthetic and Analgesic Dosages, and Intravenous Fluid Requirements in the Two Study Groups

	Control (n = 70)	Dexamethasone (n = 70)
Age (yr)	38 ± 12	34 ± 13
Weight (kg)	84 ± 25	78 ± 20
Height (cm)	156 ± 17	158 ± 14
Gender (M/F) (n)	14/56	16/54
Previous motion sickness [n, (%)]	3 (4)	0
Previous PONV [n, (%)]	7 (10)	8 (12)
History of smoking [n, (%)]	10 (14)	16 (23)
Surgery time (min)	94 ± 27	91 ± 27
Anesthesia time (min)	117 ± 33	112 ± 28
Total propofol (mg)	155 ± 35	151 ± 34
Total fentanyl (μg)	257 ± 99	254 ± 78
IV fluids (l)	1.7 ± 0.4	1.7 ± 0.5

Values are mean ± SD, or number (n) and percentages (%).

PONV = postoperative nausea and vomiting; IV = intravenous.

PONV or the complete response rate to the antiemetic prophylactic treatment between the two groups (table 3), patients in the dexamethasone group had a shorter average length of stay in the day-surgery unit and achieved discharge criteria earlier than those in the control group (table 2). In the postdischarge period, fewer patients in the dexamethasone group experienced nausea (table 3). More importantly, patients in the dexamethasone group reported higher QoR and patient satisfaction scores compared with those in the control group. None of the patients complained of confusion, depression, dysphoria, or other psychic disturbances after surgery.

In comparing the "fit for discharge" times, QoR scores, and satisfaction scores in patients who did (215 ± 89 min, 82 ± 20 mm, and 88 ± 12 mm, respectively) or did not (199 ± 70 min, 92 ± 15 mm, and 95 ± 8 mm, respectively) develop PONV, there were no statistically significant differences ($P = 0.4$, 0.2 , and 0.16 , respectively).

Table 2. Recovery Times, Time to First Analgesic and Antiemetic Rescue Medication, and Postoperative Analgesic Requirements in the Two Treatment Groups

	Control (n = 70)	Dexamethasone (n = 70)	P Value
Awakening time (min)*	6 ± 5	5 ± 6	0.67
Time to fast-track score of 12 (min)*	10 ± 7	13 ± 9	0.23
Orientation time (min)*	13 ± 8	15 ± 14	0.50
Time to Aldrete 10 (min)*	16 ± 9	16 ± 9	0.87
Oral intake time (min)*	126 ± 94	101 ± 40	0.20
Time to first rescue analgesic (min)*	63 ± 51	58 ± 62	0.42
Time to first rescue antiemetic (min)*	69 ± 34	62 ± 60	0.46
IV opioid requirement at PACU [n, (%)]	39 (56)	31 (45)	0.3
Total dose of fentanyl at PACU (μg)	32 ± 56	26 ± 34	0.3
DSU time (min)	179 ± 62	136 ± 57†	0.01
PACU time (min)	47 ± 27	52 ± 25	0.77
"Fit for discharge" time (min)*	209 ± 39	161 ± 32†	0.13
Actual discharge time (min)*	226 ± 45	189 ± 43	0.02

Values are mean ± SD, or number (n) and percentages (%); * time (min) from the end of anesthesia; † significantly different from control group, P value < 0.05.

IV = intravenous; DSU = day-surgery unit; PACU = postanesthesia care unit.

Table 3. Complete Response to Antiemetic Treatment, Incidence of Nausea and Vomiting, and Patient Satisfaction Scores in the Two Treatment Groups

	Control (n = 70)	Dexamethasone (n = 70)	P Value
Complete response to antiemetic treatment [n, (%)]	37 (53)	45 (65)	0.16
In-hospital symptoms [n, (%)]			
Nausea	34 (49)	25 (35)	0.12
Vomiting	13 (19)	6 (8)	0.3
Retching	11 (15)	6 (8)	0.19
Emetic symptoms after discharge [n, (%)]			
Nausea	20 (28)	9 (13)*	0.02
Vomiting	11 (16)	9 (13)	0.62
Patient satisfaction with PONV management (0–100)	90 ± 10	98 ± 2*	0.04
QoR (0–100)	76 ± 20	89 ± 10*	0.004

Values are mean ± SD, or number (n) and percentages (%); * Significantly different from control group, P value < 0.05.

PONV = postoperative nausea and vomiting; QoR = quality of recovery.

Discussion

In contrast to previous studies by Fujii *et al.*,^{2,3,18} which suggested that the use of dexamethasone in combination with a 5-HT₃ antagonist decreased PONV compared with either drug alone, we failed to find that the combination was any more effective than the 5-HT₃ antagonist alone in reducing the incidence of PONV. However, the adjunctive use of dexamethasone did facilitate an earlier discharge, analogous to our recent findings in an outpatient population undergoing anorectal surgery.¹⁵ More importantly, these patients also reported higher QoR scores and degree of satisfaction with the management of their PONV symptoms.

The incidence of nausea and vomiting after laparoscopic cholecystectomy remains high (22–53%) when outpatients receive prophylaxis with a single antiemetic drug.¹ In a study by Graczyk *et al.*,¹⁹ the incidence of PONV in the placebo group was 69%, whereas inci-

dences of 41–48% were reported in the groups receiving doses of intravenous dolasetron ranging from 12.5 to 50 mg. In a study by Fujii *et al.*² involving patients undergoing laparoscopic cholecystectomy, the addition of dexamethasone (8 mg) to granisetron (3 mg) reduced the incidence of PONV from 17% with the 5-HT₃ antagonist alone to 2% with the combination. However, concerns have been raised as to the reliability of these data.²⁰ In our study, the incidence of PONV was nonsignificantly reduced from 49 to 35% by the addition of dexamethasone (4 mg). However, the differences in the incidences of PONV in the various studies may be related to differences in the type of surgery, anesthesia, and patient demographic characteristics.

The 12.5-mg dose of intravenous dolasetron that we chose to study was based on the results of a cost-effectiveness analysis that suggested that this dose of dolasetron was as effective as 25 mg intravenous dolasetron and 4 or 8 mg intravenous ondansetron in preventing PONV.⁹ In the current study, 12.5 mg intravenous dolasetron was administered after removal of the gallbladder, as recommended by the manufacturer. However, the incidences of nausea (49%) and vomiting (19%) remained high. Dexamethasone has been reported to be effective for antiemetic prophylaxis in both adult and pediatric patients,^{13,21,22} with an optimal dose of 5 mg at induction of anesthesia in adults.^{23,24} Although the incidences of nausea (35%) and vomiting (8%) were lower in the dexamethasone group, this difference did not achieve statistical significance ($P = 0.1$ and 0.3 , respectively). Nevertheless, dexamethasone did facilitate the recovery process and improve patient satisfaction with their recovery after laparoscopic cholecystectomy. Analogous to our previous findings in outpatients undergoing anorectal surgery, a single 4-mg dose of dexamethasone improved the early recovery profile without significantly reducing the incidence of PONV.¹⁵ We would speculate that the mechanism responsible for the beneficial effects of dexamethasone on the recovery profile may relate to its mood altering effect and ability to produce an enhanced sense of patient well-being.²⁵

This study could be criticized because we did not include a group that received no prophylactic antiemetic drugs. However, prophylactic antiemetics are routinely administered to all outpatients undergoing laparoscopic surgery procedures at our teaching institution because of the high incidence of PONV in this patient population. Our surgical and anesthesia colleagues did not feel it was ethical to withhold all prophylactic antiemetic drugs in this high-risk outpatient population. Given this concern and our recent findings in patients undergoing laparoscopic cholecystectomy procedures,^{1,26} we felt that it was not justified to withhold all prophylactic treatment.

In a recent editorial regarding the use of surrogate outcomes in PONV studies, Fisher⁸ suggested that stud-

ies reporting incidences of nausea and vomiting were useful only if clinically meaningful endpoints (*i.e.*, post-anesthesia care unit stay, unplanned hospital admission, QoR, patient satisfaction) were influenced by the therapeutic intervention. In this study, the surrogate outcomes relating to the incidence of PONV did not achieve statistical significance. However, the clinically important outcomes relating to fitness for discharge, QoR, and patient satisfaction with their antiemetic management were significantly improved in the group receiving dexamethasone in combination with the 5-HT₃ antagonist. As true outcome measures, the improvement noted in the QoR and patient satisfaction suggests that a single 4-mg dose of dexamethasone may be a valuable adjunctive therapy during general anesthesia for adults undergoing ambulatory surgery.

In conclusion, compared with prophylaxis with dolasetron alone, patients receiving a combination of dexamethasone (4 mg) and dolasetron (12.5 mg) had an improved QoR and greater satisfaction with the management of their PONV symptoms, as well as a reduced incidence of nausea after discharge.

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