

## Sex-related differences in the efficacy of dexamethasone pretreatment for postoperative analgesia in patients undergoing laparoscopic cholecystectomy: a randomized controlled study

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**Background/aim:** Sex-related differences in response to pain have become a topic of increasing interest. However, sex-related differences in the efficacy of dexamethasone for postoperative analgesia have not been previously addressed.

**Materials and methods:** The study included 196 men and 196 women, aged between 18 and 45 years, who were scheduled for laparoscopic cholecystectomy. The patients were randomly allocated into dexamethasone (M/F: 98/98) and control (normal saline; M/F: 98/98) groups. Patients in the study group received intravenous dexamethasone at 0.1 mg/kg (dexamethasone group) 1 h before induction of anesthesia. Patients in the control group received normal saline. Changes in cumulative morphine-containing, patient-controlled analgesia consumption in both sexes, pain intensity using a visual analog scale 24 h after surgery, mean morphine consumption adjusted for body weight, and incidence of postoperative nausea or vomiting were measured.

**Results:** Women in both groups had significantly higher pain scores at 1 and 6 h postoperatively, higher levels of patient-controlled analgesia and mean morphine consumption, and more postoperative nausea and vomiting ( $P < 0.05$ ). These effects were less severe in the dexamethasone group.

**Conclusion:** The results suggest that women are less responsive than men to dexamethasone for postoperative analgesia and experience higher levels of postoperative pain.

**Key words:** Gonadal hormones, pain, sex

### 1. Introduction

Sex-related differences in pain response and response to analgesics have been increasingly studied in recent years. Research has focused on a number of physiopsychosocial factors including gonadal hormones, endogenous opioid function, genetic factors, pain coping and catastrophizing, and gender roles, which may contribute to these differences (1,2). Some authors have reported that women experience greater postoperative pain severity or diminished pain tolerance (3,4), while others have found no sex-related differences (5,6). Some evidence has supported sex-related differences in response to certain analgesic drugs, but these findings were inconsistent (3–6).

The antiinflammatory effects of dexamethasone are now known to contribute to pain relief and amelioration of nausea and vomiting (7,8). However, it has not yet been examined whether the efficacy of dexamethasone

for reducing pain intensity and opioid consumption is affected by sex or not.

This aim of this study was to investigate sex-related differences in the effects of dexamethasone pretreatment on pain intensity and morphine consumption in patients undergoing laparoscopic cholecystectomy.

### 2. Materials and methods

Ethical approval for this study (Registration No. 3658) was provided by the institutional review board of a university hospital in March 2014. Written informed consent was obtained from each participant. The study was performed at the university hospital from April 2014 to August 2016. A total of 392 patients aged between 18 and 45 years and from Class I or II of the American Society of Anesthesiologists (ASA) who were scheduled for laparoscopic cholecystectomy were included. Patients with

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hepatic and renal insufficiency, history of corticosteroid hypersensitivity, previous gastric ulcer, diabetes mellitus, and those receiving corticosteroids, immunosuppressive drugs, chronic opioids, or other analgesics were excluded.

Patients were randomly allocated to the treatment group (M/F: 98/98) and the control group (M/F: 98/98) using sealed envelopes.

On the day before surgery, all patients were taught how to use the visual analog scale (VAS) and the patient-controlled analgesia (PCA) device, and they were instructed to deliver analgesia on their own whenever they felt pain.

All patients were premedicated with intramuscular midazolam (2–3 mg) before arriving to the operating room. One hour before the induction of anesthesia, patients in the dexamethasone group received 0.1 mg/kg (5 mg/mL) intravenous (IV) dexamethasone, whereas those in the control group received IV normal saline. Monitoring including pulse oximetry, automated blood pressure (BP) cuff, electrocardiogram (ECG), and end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) with arterial and urinary catheterization was performed. Tympanic temperature was measured immediately before induction of anesthesia and again immediately before extubation.

Anesthesia induction began with a slow (30–60 s) IV bolus dose of remifentanyl (1 µg/kg), followed by propofol (1–2 mg/kg). Tracheal intubation was facilitated with rocuronium (0.9 mg/kg) and a fixed dose of remifentanyl (0.1 µg/kg per minute) was infused in both groups. Anesthesia was maintained with a desflurane 50% oxygen/air mixture. Desflurane administration was started at an end-tidal concentration of 1 minimum alveolar concentration (MAC), and the concentration was adjusted by a 1% stepwise titration according to acceptable hemodynamic limits (mean arterial blood pressure between –20% and +20% and heart rate between –20% and +20%) and to a target bispectral index (BIS) between 40 and 60.

Upon completion of surgery, the residual neuromuscular blockade was antagonized with pyridostigmine (0.2 mg/kg) and glycopyrrolate (0.008 mg/kg) when the train-of-four (TOF) ratio had returned to 25%. The patients were extubated when BIS values reached 80 and spontaneous breathing was resumed.

The PCA mixture contained morphine (60 mg), ketorolac (150 mg), and ramosetron (0.6 mg) in a total volume of 100 mL of saline. The device was set to deliver a basal infusion of 2 mL/h with bolus doses of 0.5 mL and a 15-min lockout period. Postoperative pain intensity was documented using a 100-mm linear VAS that consisted of a straight line, with the left end of the line representing no pain (0) and the right end of the line representing the worst pain (100). During postanesthesia recovery, patients

with VAS scores of  $\geq 40$  received 30 mg of IV ketorolac with an additional dose of 15 mg, if needed. Postoperative VAS score on exertion was measured at 1, 6, 12, and 24 h from the time of initial arrival at the postanesthesia care unit.

The primary outcome was changes in cumulative morphine-containing PCA consumption in both sexes. The secondary measures were VAS scores on exertion at 1, 6, 12, and 24 h after surgery; mean morphine consumption adjusted by body weight; time to first postoperative analgesic requirement; and any episode of postoperative nausea or vomiting (PONV). PONV was treated with IV ondansetron (4 mg).

### 2.1. Statistical analysis

A preliminary investigation showed that the means of cumulative PCA morphine consumption in women and men were 63.85 and 61.95 mL, respectively, with a standard deviation (SD) of 6.17 and 6.58. Considering power of 80% and an  $\alpha$ -coefficient of 0.05 for cumulative PAC consumption of morphine in women compared to men in each group, the sample size was calculated as 178 samples for each group. Assuming a 10% dropout rate, the final sample size was determined to be 196 patients per group (98 men and 98 women). The statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The results are presented as mean  $\pm$  SD or as number of patients (%). Means between groups and between women and men within groups were conducted using the independent t-test, and categorical data were evaluated using chi-square tests. Significance was defined as  $P < 0.05$ .

### 3. Results

Twelve of the total 392 patients that were included in the study were withdrawn from the final analysis because of conversion to open surgery or reexploration for postoperative bleeding. Of the 380 remaining patients, 191 were in the control group and 189 were in the dexamethasone group.

There were no significant differences between two groups with respect to age, sex, weight, and duration of surgery (Table 1).

Compared to the controls, patients in the dexamethasone group had lower cumulative PCA consumption, mean morphine consumption adjusted for body weight, and rescue analgesia (ketorolac) requirements ( $P < 0.05$ ). Additionally, patients in the dexamethasone group had lower VAS pain scores on exertion at 1, 6, and 12 h postoperatively; a lower incidence of PONV and antiemetic (ondansetron) required; and a significantly longer time to first postoperative analgesic dose than those in the control group ( $P < 0.05$ ) (Table 1).

On comparison by sex, women in both the dexamethasone group and the control group had

**Table 1.** Patient characteristics.

	Control group (n = 191)	Dexamethasone group (n = 189)
Age (years)	40.9 ± 2.4	40.3 ± 4.0
Weight (kg)	63.5 ± 6.9	64.4 ± 6.7
Sex (male/female)	97/94	94/95
Time of surgery (min)	58.0 ± 8.6	58.0 ± 8.8
Time to first postoperative analgesic administration (min)	34.9 ± 8.9	39.1 ± 8.6*
Cumulative PCA consumption (mL)	64.4 ± 50.3	61.0 ± 6.0*
Mean morphine consumption (mg/kg)	0.61 ± 0.08	0.58 ± 0.08*
Pain intensity with effort		
VAS, 1 h	46.8 ± 9.7	42.5 ± 8.4*
VAS, 6 h	41.6 ± 8.0	36.4 ± 7.8*
VAS, 12 h	31.4 ± 7.1	28.0 ± 5.9*
VAS, 24 h	22.9 ± 6.7	22.6 ± 4.6
Ketorolac consumption (mg)	37.6 ± 7.7	35.2 ± 7.1*
Postoperative nausea or vomiting	68 (35.6)	45 (23.8)*
Antiemetic requirement	62 (32.5)	69(20.6)*

Values are expressed as mean ± SD or number (%) of patients. VAS: Visual analog scale, PCA: patient-controlled analgesia. \*: P < 0.05 vs. control group.

significantly higher VAS pain scores with exertion at 1 and 6 h, and greater mean morphine consumption with a higher incidence of PONV and antiemetic (ondansetron) required during 24 h (P < 0.05). Women in both groups had shorter time to first postoperative analgesic requirement (P < 0.05). Men in the control group had greater cumulative PCA consumption during 24 h after surgery than women, but the difference was not significant. In the dexamethasone group, women had higher cumulative consumption of PCA in 24 h compared to men (P < 0.05) (Table 2).

#### 4. Discussion

The strong antiinflammatory properties of dexamethasone have been associated with its efficacy when used for postoperative analgesia. Although the analgesic mechanism of dexamethasone has not been fully elucidated, it appears that a decrease in cyclooxygenase and lipooxygenase production, via inhibition of peripheral phospholipase, plays a main role (7–9).

Several recent investigations have reported the potential analgesic benefit of dexamethasone. However, they showed inconsistent findings, which resulted from

variability in the type of surgery, dexamethasone dose and timing, anesthetic regimen, and type of postoperative rescue analgesic (7). However, these previous studies have not considered sex-related differences in dexamethasone efficacy.

Our study has shown that women undergoing laparoscopic cholecystectomy had higher postoperative VAS pain scores with exertion levels of pain, greater mean morphine consumption when corrected for body weight, and shorter time to first postoperative analgesic dose administration than men. Sex-related differences in pain response and opioid susceptibility remain a matter of debate. Some studies have reported that men have higher pain thresholds and greater pain tolerance for all types of noxious stimuli than women (3,4). However, other studies have shown no significant differences in pain scores between men and women (5,6). Several other studies have consistently supported the existence of sex-based differences in pain modulation between men and women. Therefore, sex could be an important consideration in providing optimum analgesia (1–4,10).

Women in both groups consumed a proportionally larger amount of morphine when adjusted for body

**Table 2.** Comparison of pain scores, morphine consumption, and postoperative nausea or vomiting in men and women.

	Control group		Dexamethasone group	
	Men (n = 97)	Women (n = 94)	Men (n = 94)	Women (n = 95)
Time to first postoperative analgesic requirement (min)	36.0 ± 9.5	33.7 ± 8.2*	41.6 ± 7.7	36.5 ± 8.6*
Cumulative PCA consumption (mL)	64.8 ± 4.8	64.0 ± 5.3	60.2 ± 6.2	61.9 ± 5.6*
Mean morphine consumption (mg/kg)	0.57 ± 0.06	0.66 ± 0.07*	0.53 ± 0.07	0.62 ± 0.07*
Pain intensity with effort				
VAS, 1 h	45.3 ± 9.6	48.4 ± 9.5*	40.1 ± 8.7	44.8 ± 7.4*
VAS, 6 h	40.4 ± 6.9	42.8 ± 8.8*	33.7 ± 7.0	39.1 ± 7.6*
VAS, 12 h	31.3 ± 6.6	31.5 ± 7.8	27.7 ± 5.4	28.3 ± 6.5
VAS, 24 h	22.9 ± 6.1	22.9 ± 7.3	22.6 ± 4.6	22.6 ± 4.7
Postoperative nausea or vomiting for 24 h	23 (23.8)	45 (48)*	15 (16.0)	30 (31.6)*
Antiemetic required	20 (21.6)	41 (43.6)*	10 (10.6)	29 (30.5)*

Values are expressed as mean ± SD or number (%) of patients. VAS: Visual analog scale (0 to 100), PCA: patient controlled analgesia.  
\*: P < 0.05 vs. men.

weight. This is in line with most recent studies, which have reported that the potency and efficacy of morphine is greater in men than in women over a variety of nociceptive modalities (11,16). When studies are performed using PCA in a postoperative setting, sex-based differences in pain response and analgesic efficacy may be confounded by psychological factors or personality traits, or particularly by opioid side effects such as PONV, which may affect the frequency of PCA administration and the degree of pain intensity and pain relief.

In our results, sex-related differences remained even after correcting for body weight, suggesting that the differences may be due to gonadal hormones such as estrogen and testosterone, in addition to subjective or psychosocial factors that may affect pain behaviors (1). The findings suggesting diminished analgesic efficacy of dexamethasone in women in our study may further support a role for gonadal hormones in analgesia response. It has been found that dexamethasone acts directly on the pituitary gland to suppress the action of estradiol and lowers circulating estrogens (17,18). Gonadal hormones are associated with modulating pain intensity (19). A decrease in pain threshold and an increase in morphine consumption has been found in women with menstrual cycles, notably during the luteal phase (19,20). Our study also showed that the potential postoperative antiemetic effects of dexamethasone in women were greater than in men (reduction rate of PONV 16.4% vs. 7.8%). The apparent sex-based difference in the

efficacy of dexamethasone against PONV may also be related to gonadal hormones. Estradiol may sensitize the chemoreceptor trigger zone or the vomiting center of the brain. Taken together, the interaction between gonadal hormones and dexamethasone may exist in pain control and morphine sparing (20–22).

A limitation of this study was that we did not consider the hormonal state of the women or the stages of their menstrual cycles. Thus, this could be another possible uncontrolled confounding factor of the difference in the results. Another possibility is that women simply reported their pain more readily, whereas men were underreporting.

In conclusion, the mechanistic basis for sex-related differences in pain response and analgesic efficacy is not entirely understood; however, sex hormones are thought to be an influencing factor. An improved understanding of the mechanisms underlying sex-related differences in pain perception and response to analgesic drugs should permit improved pain management strategies for postoperative patients. Although the observed sex-related differences in opioid effects may be clinically relevant, the lack of knowledge about other factors involved in the large variability of patient opioid analgesic sensitivity should compel practitioners to customize their dosing regimens based on individual requirements.

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