

# Effect of gender on pain perception and analgesic consumption in laparoscopic cholecystectomy: An observational study

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## Abstract

**Background:** Evidence regarding gender affecting the response to pain and its treatment is inconsistent in literature. The objective of this prospective, observational study was to determine the effect of gender on pain perception and postoperative analgesic consumption in patients undergoing laparoscopic cholecystectomy.

**Materials and Methods:** We recruited 60 male and 60 female patients undergoing elective laparoscopic cholecystectomy. Patients were observed for additional intraoperative and postoperative analgesia. Numerical rating scale was documented at 10 min interval for 1 h in post-anesthesia recovery room and at 4, 8, and 12 h postoperatively. Boluses of tramadol given as rescue analgesia were also noted. There were no dropouts.

**Results:** The mean pain scores were significantly higher in female patients at 20 and 30 min following surgery. Mean dose of tramadol consumption was significantly higher in female patients for the first postoperative hour ( $P = 0.002$ ), but not in the later period.

**Conclusion:** Female patients exhibited greater intensity of pain and required higher doses of analgesics compared to males in the immediate postoperative period in order to achieve a similar degree of analgesia.

**Key words:** Gender difference, pain perception, postoperative analgesia, opioids

## Introduction

Gender difference in pain perception and efficacy of pain medication between males and females has been increasingly studied in recent years.<sup>[1]</sup> In several randomized clinical trials females have been shown to experience greater intensity of postoperative pain and less tolerance to pain compared to men.<sup>[2]</sup> Evidence also exists in literature regarding gender difference in response to opioids, but the findings are inconsistent.<sup>[3]</sup> Some studies show that female patients experience greater analgesic efficacy compared to males following administration of mixed opioid agonist antagonists, whereas other studies with morphine demonstrate that women require a higher drug

dose compared to males in order to achieve analgesia of the same degree. There are also reports on gender difference in response to nonopioid analgesics.<sup>[4]</sup>

There is need for further studies in different populations to see the effect of gender on both intensity of pain and analgesic requirements and this might help to modify the practice of prescribing analgesic medication according to gender. The objective of our study was to determine if there was a difference between males and female patients in the perception of pain or its intensity and tramadol requirement following laparoscopic cholecystectomy.

## Materials and Methods

This was a prospective, observational study conducted between August 2006 and July 2009. Ethical approval was provided by the Ethical Committee of the University (Ethical Committee No: 490-Ane/ERC-07). Written informed consent was taken from all patients. One hundred and twenty American Society of Anesthesiologists (ASA) I and II patients (60 males and 60 females), aged 20–60 years undergoing elective laparoscopic cholecystectomy under general anesthesia were enrolled. Exclusion criteria was patients suffering from acute cholecystitis, empyema or malignancy of gall bladder, history of

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chronic pain or those taking regular analgesics preoperatively, peptic ulceration, bleeding disorders, impaired renal or hepatic function, and sensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids. Patients unable to understand instructions or having communication problems were also excluded from the study.

Preoperatively, all patients were instructed regarding the use of numerical rating score (NRS) for postoperative pain assessment (from 0 = no pain to 10 being the most excruciating pain imaginable). The patients were also instructed to indicate the degree of pain improvement on a 5 point Likert scale (no improvement, minimal, moderate, very much, or complete pain relief) after receiving an analgesic medication.

All patients received premedication with oral midazolam 7.5 mg, 0.5–1 h preoperatively. On arrival in the operating; room routine monitoring, that is, electrocardiogram, noninvasive blood pressure (BP), and pulse oximetry was instituted, using Datex AS/3 monitor (Helsinki, Finland). Baseline readings of systolic, diastolic, and mean BP; heart rate; and oxygen saturation were obtained after a resting period of 5 min.

Anesthesia was induced with intravenous (IV) fentanyl 1.5  $\mu\text{g kg}^{-1}$ , propofol 2 mg  $\text{kg}^{-1}$ , and atracurium 0.6 mg  $\text{kg}^{-1}$ . After tracheal intubation, patient's lungs were mechanically ventilated and anesthesia was maintained with 60% nitrous oxide, oxygen, and one minimum alveolar concentration (MAC) isoflurane. A further bolus of fentanyl 50  $\mu\text{g}$  was given after 45 min of the initial dose or earlier if heart rate or BP increased by more than 20% of baseline value after incision. A rectal suppository of diclofenac 100 mg was inserted after completion of surgery and before extubation. At the end of the surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.5 mg.

On arrival in post-anesthesia care unit (PACU), routine noninvasive monitoring (ECG, BP, respiratory rate, and oxygen saturation) was started. One of the investigators asked the patients to rate their baseline pain on the NRS. Patients were given IV tramadol 10 mg if NRS was between 3 and 5 and 20 mg if NRS was more than 5 until their pain intensity reduced to less than 3. During the stay in the PACU, patients were asked to rate their pain intensity on NRS every 10 min and to indicate the degree of improvement on Likert scale. If pain did not settle after 50 mg of tramadol, IV morphine in 2 mg boluses was used as additional rescue analgesia. The patients were kept in PACU for 60 min postoperatively and then shifted to the ward provided NRS was less than 3.

Any side effects like nausea, vomiting, sedation (unrousable

sleep), or respiratory depression (respiratory rate less than 8) was recorded. The level of sedation was assessed by using the sedation score described by Chernik, *et al.*, that is, 0 = awake, 1 = sleeping comfortably and responding to vocal commands, 2 = somnolence, deep sleep but responding to vocal commands, and 3 = not arousable, deep sleep.<sup>[5]</sup> Persistent nausea (defined as feeling of nausea for more than 30 min) and vomiting more than twice was treated with IV metoclopramide 10 mg bolus. Patients were similarly assessed at 4, 8, and 12 h postoperatively in the ward. The study ended after 12 h. The post-anesthesia assessments were conducted by a resident unconnected with the study who was unaware that the study was being conducted to look at the influence of gender on pain.

### Statistical analysis

The minimum sample size required in each group was calculated as 60. This was based on the hypothesis that a 20% difference in pain perception and analgesic consumption exists between genders at a 5% significance level and 80% power with a 0.5% standard deviation (SD). The maximum correlation detected by parametric/nonparametric test between measurements on the same subject was assumed to be 0.9.

The data was double entered in Epi Data (version 3.1) and verified for data entry errors. An error rate of less than 3 per 1,000 was considered valid data entry. Mean, SD by gender, and 95% confidence interval for difference in mean were observed for age, weight, duration of study, and intraoperative fentanyl usage. Repeated measures of analysis of variance (ANOVA) were conducted to see the association within group at different times and between groups (males and females) for heart rate and systolic and diastolic BPs. Comparison between groups, for ASA status, nausea, vomiting, antiemetic requirement, and rescue analgesia usage were compared by using the chi-square test.

Independent samples *t*-test was used to observe the mean difference by gender for age, weight, duration of surgery, intraoperative fentanyl usage, pain assessment, degree of pain improvement, and consumption of tramadol during 12 h postoperatively. A *P*-value of less than 0.05 was considered statistically significant.

## Results

One hundred and twenty patients were enrolled into and completed the trial. There were no dropouts.

### Demographic characteristics

Table 1 shows the demographic details; no significant difference was observed for age, ASA status, and duration

of surgery [Table 1]. Female patients had a lower mean weight compared to males (mean difference: 9.0; 95% CI: 4.5–13.5,  $P$ -value < 0.001).

### Intraoperative analgesia

Fifty-four males and 59 females required additional fentanyl boluses intraoperatively ( $P$ -value 0.654).

### Postoperative analgesia and complications

#### Recovery room

The baseline pain score (NRS) was similar in both males and females. Six readings at 10 min interval were taken in the recovery room [Figure 1]. Mean pain scores were significantly higher in female patients at 20 and 30 min following surgery. The mean dose of tramadol consumption during the 1<sup>st</sup> h in the recovery was 40 mg (SD 26.5) in females and 27.8 mg (SD 24.5) in the male patients. This difference was significant ( $P = 0.01$ ). Twenty-one females (35.0%) and 19 males (31.7%) required tramadol boluses during the 1<sup>st</sup> h in recovery. Morphine 1 mg bolus was used as further rescue analgesia. The mean dose of morphine during the 1<sup>st</sup> h in recovery was 1.57 (SD 1.65) mg in females and 0.63 (SD 1.58) mg in the male patients. This difference was also significant ( $P = 0.002$ ). Seven female patients and four male patients had postoperative nausea and vomiting during their stay in PACU.

**Table 1: Demographic characteristic, duration of surgery, American Society of Anesthesiologists physical status and mean dose of fentanyl used intraoperatively**

Variables	Females (n=60) Mean (SD)	Males (n=60) Mean (SD)	95 % Confidence interval of the mean difference Mean difference (LCI, UCI)
Age; years	42.8 (10.3)	45.0 (10.1)	2.2 (-1.6, 5.8)
Weight; kg	67.7 (13.3)	76.7 (11.5)	9.0 (4.5, 13.5)*
Duration of surgery; min	96.6 (33.8)	108.1 (40.2)	11.5 (-1.9, 25.0)
ASA grade			
I	28 (46.7%)	33 (55.0%)	
II	32 (53.3%)	27 (45.0%)	

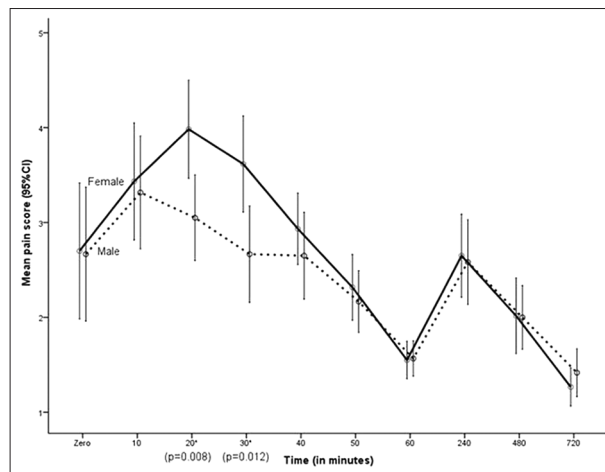
ASA = American Society of Anesthesiologists, SD = standard deviation, LCI and UCI indicates lower and upper confidence intervals for the mean difference; \* Significant difference

**Table 2: Tramadol boluses administered during the 12 h post-operative period**

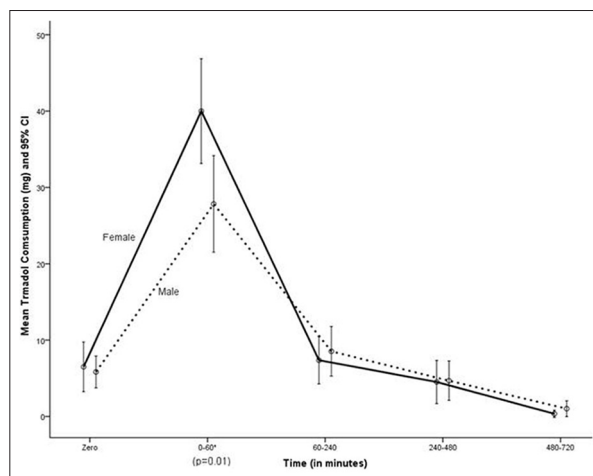
Total number of boluses	Females (n=60)	Males (n=60)	P value
0	1	6	
1	20	13	
2	23	18	0.654
3	10	20	
4	6	3	

### Ward

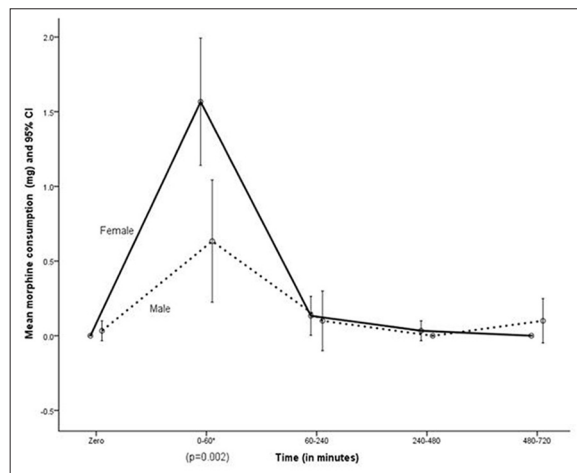
There was no difference in the mean pain scores between the male and female patients at 4, 8, and 12 h postoperatively.



**Figure 1:** Postoperative pain score (NRS) in male (o) and female (●) patients



**Figure 2:** Tramadol consumption in postoperative period in male (o) and female (●) patients



**Figure 3:** Morphine consumption in the postoperative period in male (o) and female (●) patients

Mean consumption of tramadol during 60–240, 240–480, and 480–720 min was the same in the two groups [Table 2]. The total dose of tramadol (SD) consumed in 12 h was higher in the females 58.7 (33.8) mg as compared to males 47.9 (40.01) mg, but this did not reach statistical significance ( $P = 0.11$ ) [Figure 2].

There was no difference seen in the mean dose of morphine used during the above specified periods between the two groups, however females had a larger mean consumption 1.73 (SD 1.82) mg versus 0.87 (SD 2.34) mg in males ( $P = 0.025$ ) in order to achieve a NRS score of less than 3 [Figure 3]. Thirty-three female patients (55%) and 12 male patients (20%) required morphine rescue analgesia during the study period. This was statistically significant ( $P < 0.001$ ).

Postoperative nausea and vomiting was the only complication seen in 11 (18.3%) of female patients and in six (10.0%) male patients during the study period ( $P = 0.191$ ).

None of the patients had a sedation score of more than two or a respiratory rate of less than 8 breaths/min.

## Discussion

In this prospective, observational study of 120 patients (60 males and 60 females), we have observed that females had significantly higher pain scores during the 1<sup>st</sup> h after surgery and required higher doses of opioid in order to achieve a similar degree of pain relief following laparoscopic cholecystectomy, compared to a group of male patients.

There are several theoretical reasons that can lead to gender difference in pain perception and its management. Firstly, it could be attributed to a different socialization process for men and women, which influences bodily experience and the willingness to communicate distress.<sup>[6]</sup> Secondly, hormonal variation can also lead to gender difference in pain experience and response to analgesia. Gonadal hormones are known to modulate pain intensity and influence sensitivity to opioid analgesics. During luteal phase of menstrual cycle a decrease in pain threshold and increase in opioid consumption has been reported. Gender-related difference has been shown to disappear in elderly patients, this also favors the impact of gonadotrophic hormones on difference in pain.<sup>[7]</sup> Thirdly, women have greater body fat percentage than males. Opioids are more lipophilic, therefore the plasma concentration could be less in females. None of the studies has taken into account the pharmacokinetics of opioid, that is, the blood levels of opioid at different time intervals and its relationship to pain scores.<sup>[8]</sup>

Previous studies addressing influence of gender on pain perception and the requirements of analgesics for pain relief to similar degree of analgesia have reported conflicting results. This could be due to heterogeneity in studies with respect to type of analgesic drugs, type of surgery, different methods of pain relief, end point of treatment, duration, and ethnicity. In a study by Chia, *et al.*, males had increased postoperative pain and morphine requirements;<sup>[9]</sup> but in contrast, greater pain among females have been reported after collectively studying different surgical procedures.<sup>[6,7,10]</sup> No difference in pain scores based on gender in the immediate postoperative period was reported in patients undergoing arthroscopic knee joint surgery; but during the first postoperative day, scores were higher in females as compared to males.<sup>[11]</sup> Rosseland and Stubhaug stated that greater percentage of females reported pain as compared to males in patients undergoing knee arthroscopic surgery, but there was no difference in pain scores between the groups.<sup>[12]</sup> Pain scores at rest were also significantly higher in females compared to males in a study of acute pain following endoscopic hernioplasty.<sup>[13]</sup>

In order to standardize the surgical procedure, we chose laparoscopic cholecystectomy since it is a commonly performed procedure universally. Pain is the most frequent complaint leading to delayed discharge after laparoscopic cholecystectomy.<sup>[14,15]</sup> During our literature search, we came across only one study by Uchiyama, *et al.*, that had focused on gender difference in postoperative pain following this procedure.<sup>[16]</sup> Their results were similar to our study and pain scores were significantly and consistently higher in females than males. In contrast to our study, use of postoperative analgesia was not standardized and they used either nonsteroidal anti-inflammatory suppository or weak opioid intramuscularly, whereas our patients were administered a standardized dose of opioid by IV route.

Our study has certain limitations. Blinding was not possible because of the nature of the study, and this could be a possible source of bias as gender role expectations can influence observer's ratings of pain.<sup>[17,18]</sup> Weight of male patients was significantly greater than females and this could be the reason for increased use of intraoperative fentanyl. Postoperatively, we used a fixed dose of diclofenac irrespective of the patient's weight. The weight of the female group was less than the males, but in spite of this they exhibited higher pain scores on NRS. This goes more in favor of weight not affecting the opioid requirements, but shows the effect of gender which influenced the intensity of pain and requirements of analgesic drugs. We also did not consider the hormonal state of the females and stage of menstrual cycle, thus this could be another possible uncontrolled confounding factor for difference in results.<sup>[19]</sup> Although females experienced more pain and

consumed more opioid, the decrease in pain was similar after 30 min postoperatively. Another possibility is that females simply reported their pain at a higher level, whereas males were underreporting it.

In conclusion female patients exhibited greater intensity of pain and required higher doses of analgesics compared to males in order to achieve a similar degree of analgesia during the first postoperative hour. This has implications for future research. As gender contributes as an important factor in effective pain management, then this factor should be considered in selection of patients in randomized clinical trials involving pain, and this difference should have implications for treatment of pain in female patients.

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