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ORIGINAL SCIENTIFIC REPORT

Gender Differences in Postoperative Pain, Nausea and Vomiting After Elective Laparoscopic Cholecystectomy

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Abstract

Background Although reports suggest that pain and postoperative nausea and vomiting (PONV) may be more frequent in women, the evidence is inconsistent. The objective of this study was to investigate whether women are more sensitive to pain and PONV after laparoscopic cholecystectomy (LC).

Methods A total of 370 women and 275 men were included in a retrospective cohort study. All underwent LC under standardized general anesthesia. The variables analyzed included clinical and anthropometric parameters. End points were the incidence of nausea, vomiting, pain, and the requirement for additional pain relievers and antiemetics to control these.

Results The women were younger and had lower body weight than the men ($p < 0.001$). Body mass index was within the normal range for 50% of women and 30% of men ($p < 0.001$). Pain was more common in women at 1, 6, 12 and 24 h after surgery ($p < 0.02$). Narcotics in addition to the doses used to lessen pain intensity ($p = 0.01$) were required in 60 women and 19 men ($p < 0.001$). PONV was more frequent in women at 1 and 6 h after surgery ($p < 0.01$). Rescue antiemetics were required in 35 women and 11 men ($p = 0.008$). Hospital stay was shorter for men ($p < 0.001$). Four patients in each group developed postoperative complications ($p = 0.14$). There was no mortality.

Conclusions Early postoperative pain, nausea and vomiting after LC were more common in women, who more frequently required analgesic and antiemetic rescue medication.

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Introduction

Laparoscopic cholecystectomy (LC) is one of the procedures most widely performed by general surgeons and is the benchmark treatment for cholelithiasis, a disease for which Mexico has the third-highest prevalence in Latin America after Chile and Bolivia. The prevalence is 14.3%, 8.4% in men and 20.4% in women [1–3]. Postoperative pain, nausea and vomiting are known to be one of the most common complications after any surgical procedure. The incidence of postoperative nausea and vomiting (PONV) ranges between 46 and 72%, and despite advances in the last decades in terms of understanding the pathophysiology of pain and PONV, and the improvement in minimally invasive techniques, these symptoms persist [4, 5]. Kapur [6] and Fisher [7] defined them as "the big little problem."

The original work by Apfel and his collaborators established four predictors for the development of PONV: female gender, history of motion sickness, not smoking, the use of postoperative opioids and age < 50 years. If none, one, two, three or four of these risk factors were present, the incidence of PONV was 10%, 20%, 40%, 60% or 80% [8]. Strategies to reduce its incidence are related to the use of intraoperative prophylactic antiemetics and the judicious use of narcotic analgesics. However, intravenous narcotics can induce intolerance to the oral route because of nausea and vomiting. [9–12].

For several years, gender differences have been studied as a risk factor for PONV and pain. Some studies, such as that by Hussain et al., reported that women present with greater nausea, vomiting and pain in the immediate postoperative period [13]. In contrast, Theodoraki et al. [14] reported that there was no difference in PONV between men and women undergoing a range of abdominal procedures.

Because of this conflicting evidence concerning the association between gender and pain and PONV, the present study attempted to elucidate the differences between the incidence of these effects in men and women, to provide a better understanding of postsurgical treatment and eventually to allow individualized gender-based management after minimally invasive procedures.

Patients and methods

Patients

This retrospective cohort study was conducted according to the STROBE guidelines for observational studies [15]. It included 645 patients with symptomatic cholelithiasis, scheduled for elective LC between January 2013 and December 2019.

Patients in classes III and IV of the American Society of Anesthesiologists (ASA) criteria were excluded. Other exclusion criteria were age 65 years and over, pregnant women, history of motion sickness, steroid treatment, uncontrolled diabetes mellitus (hemoglobin A1c > 8%), use of opioids, sedatives or any pain reliever one week before surgery, history of alcohol or drug abuse, a preoperative diagnosis of acute cholecystitis, acute pancreatitis, choledocholithiasis, or gallbladder carcinoma, and conversion of LC to an open procedure. Patients were followed from hospital admission until 30 days after surgery.

Anesthesia and surgery

All patients underwent a standardized general anesthesia procedure. The induction used intravenous midazolam (1.5 mg) fentanyl (3–5 mg/kg body weight) and propofol (2 mg/kg body weight). Anesthesia was maintained with 2% to 3% sevoflurane and 100% oxygen. Neuromuscular blockade was maintained with intravenous vecuronium (0.1 mg/kg body weight). All patients were monitored with indirect measurements of blood pressure and heart rate using standard techniques, plus exhaled CO_2 content and oxygen saturation in the blood. After surgery, all patients were extubated and transferred to the immediate postsurgical care unit with cardiovascular and oxygen monitoring. All received preoperative intravenous antibiotics (1 g of first-generation cephalosporin) and intravenous antiemetic prophylaxis with 8 mg ondansetron. LC was performed using a four-trocar, two-hand technique with two 10-mm ports and two 5-mm ports. The umbilical port was introduced by the open method to create a pneumoperitoneum, maintained at 12–14 mmHg of intraabdominal pressure.

Closed suction drains were placed according to surgeons' preferences. Morbidity was classified using the Clavien–Dindo classification [16].

Analgesia and antiemetics

Pain, nausea and vomiting were assessed immediately upon return to the recovery room, and at 6, 12 and 24 h postoperatively using a 10-point visual numerical rating scale (NRS), with 0 indicating no pain and 10 for maximum pain. This scale classifies the intermediate values as mild (1–3), moderate (4–6) and severe (7–9) pain, with 10 for excruciating pain [17, 18].

Analgesia was administered as intravenous sodium ketorolac (30 mg every 8 h). Intravenous tramadol infusion at a dose of 50 mg diluted was used as a back-up analgesic. The incidence of PONV was recorded at the same monitoring times. Intravenous ondansetron (4–8 mg) was

administered on-demand according to the surgeon's preference.

Data collection

Morbidity was recorded and patients were followed up to 30 days after discharge. The data collected also included patient age, gender, body mass index (BMI), ASA score, previous abdominal surgeries, operative time and length of hospital stay. The end points of the study were nausea, vomiting, pain, and administration of additional narcotics and antiemetics.

Sample size

Lee et al. [19] reported that the incidence of PONV was 48% in women and 24% in men, and that moderate to severe pain occurred in 32% of women and 16% of men. Therefore, we chose the lowest incidence (16%) for calculation of the required sample size with a difference of proportions formula. The alpha error was set at 0.05 and the beta error at 0.90. A minimum of 250 female and 125 male patients were required.

Statistical analysis

The statistical analysis was performed using SPSS (v 22 for Windows, IBM Corp., Armonk, NY, USA). It was divided into a descriptive phase, in which the qualitative and quantitative variables were expressed as raw numbers, proportions and mean ± standard deviation, and an analytical phase. Levene's test of homogeneity of variances showed that the results for the continuous quantitative variables were normally distributed, so Student's *t* test was used to analyze quantitative variables and the Chi square test or Fisher's exact test for qualitative variables. All p values < 0.05 were considered significant.

Ethical considerations

The study was conducted in accordance with the principles of the 1989 Declaration of Helsinki and its amendments and with the Mexican Health Guidelines. The Ethics and Research Committees of the Specialties Hospital of the Mexican Institute of Social Security in Jalisco, Mexico, approved all protocols with the registration number R-2020-1301-074.

Results

A total of 370 women and 275 men were included in the study. The clinical characteristics of the patients are described in Table 1. The women were younger and had lower body weight than men ($p < 0.001$). The BMI was within the normal range in 50% of women but in only 30% of men ($p < 0.001$).

Previous abdominal surgeries were commonest in women (10%), mainly because of bilateral tubal occlusion. Only 6% of male patients had undergone previous procedures ($p < 0.001$). ASA score distribution was similar in both groups, being ASA I in 60% of both cohorts ($p = 0.26$). The operative time was greater than 80 min with no difference between groups ($p = 0.16$). Closed drains were placed in 20 women and 16 men, which were removed 24 to 36 h after surgery.

Pain was significantly more common in the women, starting from the first hour up to 24 h after surgery; the pain intensity was as shown in Table 2. Fortunately, most patients reported only mild to moderate pain. Severe pain was reported by 15% of women during the first hour and by 2% at 6 h after surgery. Only 7 (2.5%) men reported severe pain during the first hour ($p < 0.001$).

Additional narcotic medication was required in 60 women (16.2%) and 19 men (6.9%). This difference was significant ($p < 0.001$) as was the total number of narcotic doses used to lessen pain intensity ($p = 0.01$). Of the 60 women who required additional narcotics, 45 (75%) were younger than 50 years of age and 15 (25%) older than 50 years ($p = 0.025$). The average dose of additional narcotics was 70.2 ± 24.7 mg and 52.6 ± 11.5 mg, respectively, in these two groups ($p = 0.004$).

The incidence of PONV was higher at 1 h and 6 h after surgery in women. Thirty-five women (9.5%) required rescue antiemetic medications in contrast to 11 (4%) men ($p = 0.008$). A detailed description of the characteristics of PONV is shown in Table 3. A similar proportion of younger and older women required additional antiemetics ($p = 0.8$) and the mean additional doses were 9.5 ± 4 mg and 10.4 ± 2.2 mg, respectively ($p = 0.61$).

The length of hospital stay was shorter for men than for women ($p < 0.001$), but all patients were discharged on average the day after surgery. Four patients in each group developed postoperative complications ($p = 0.14$). Two women required percutaneous drainage because of bile collections. Biliary injuries were ruled out using endoscopic retrograde cholangiopancreatography. The other complications were classified as Clavien–Dindo II. There was no mortality during the 30-day follow-up period.

Table 1 Baseline characteristics of male and female patients

	Women (n = 370)	Men (n = 275)	p value
Age (years)	39.4 ± 7.9	47.4 ± 8.8	0.000
Range (years)	(19–65)	(25–65)	
< 50 years	313 (85%)	153 (56%)	0.000
> 50 years	57 (15%)	122 (44%)	
Weight (kg)	68 ± 7.5	73.8 ± 6.4	0.000
Height (m)	1.63 ± 0.05	1.66 ± 0.06	0.000
BMI (kg/m^2)	25.3 ± 2.5	26.8 ± 2.7	0.000
< 25 kg/m^2	187 (50.5%)	83 (30%)	0.000
> 25 kg/m^2	183 (49.5%)	191 (70%)	
Previous abdominal surgery	37 (10%)	16 (6%)	0.000
Bilateral tubal occlusion	22	–	
Appendectomy	5	6	
Hiatal hernioplasty	4	3	
Inguinal herniorrhaphy	2	6	
Sigmoidectomy	2	1	
Lipectomy/abdominoplasty	2	–	
ASA I/II	211/159	169/106	0.26
Operative time (min)	83.2 ± 7.3	84 ± 1.8	0.16
Closed drainage	20 (5.4%)	16 (5.8%)	0.82
Hospital stay (h)	22.1 ± 3.2	20.9 ± 1.8	0.000
No morbidity (%)	366 (99%)	271 (98.5%)	
Clavien–Dindo morbidity II/III	2/2	4/0	0.14

Discussion

This is the first study conducted in Mexico that has attempted to explore the incidence of PONV as well as pain and its intensity in men and women treated with minimally invasive surgery for symptomatic cholelithiasis. The results reveal that during the first 6 h after surgery, PONV was more common in women, as was pain that persisted during the 24 h after surgery. However, the cohorts were not homogeneous because the men were older than the women and their physical constitution contributed to a higher BMI. This may be a consequence of the higher prevalence of symptomatic cholelithiasis in women and therefore its earlier occurrence [1, 2].

Eighty-five percent of our female cohort was under 50 years of age. Those over 50 years of age required fewer doses of narcotics at a significantly lower total dose. We did not observe any difference in PONV between these age groups. Fifty is the average age at which Mexican women become postmenopausal. Hormone levels play an important role in the perception of differences in pain experience and the response to analgesia. Gonadal hormones modulate pain intensity. Even the response to pain in women varies depending on age and menstrual cycle [20–22].

Although cholelithiasis is a quite common disease and LC is considered the gold standard for surgical treatment [3], the published scientific evidence concerning PONV is scarce. In 1998, Dabbous et al. [23] reported the results of a clinical trial comparing the incidence of vomiting in patients scheduled for elective cholecystectomy and the effect of two antiemetic preventive drugs: ondansetron and metoclopramide. With a study population of 53 women and 32 men, their results demonstrated a general incidence of postoperative vomiting of 18.9% in women compared with 0% incidence in men.

In 2006, Uchiyama et al. [24] published a prospective observational study that evaluated the effect of sex as a risk factor for postcholecystectomy pain. They recruited a total of 46 men and 54 women aged < 80 years. For pain evaluation they employed a visual analog scale (VAS) at 6, 24, 48, 72 and 96 h postsurgery. Their results indicated that at 6 h postsurgery, the pain levels in both sexes were similar; however, at 24 h, women suffered more frequent and more intense pain than men.

Table 2 Postoperative pain measured with NRS in female and male patients

	Women (n = 370)	Men (n = 275)	p value
Postoperative pain			
NRS 1 h	4.6 ± 2	3.6 ± 1.6	0.000
NRS 6 h	4 ± 1.4	2.9 ± 1.1	0.000
NRS 12 h	2.8 ± 0.8	2.3 ± 0.8	0.000
NRS 24 h	1.1 ± 0.7	0.9 ± 0.7	0.012
Pain intensity 1 h			
Mild (NRS 1–3)	100 (27%)	121 (44%)	0.000
Moderate (NRS 4–6)	214 (58%)	147 (53.5%)	
Severe (NRS 7–9)	56 (15%)	7 (2.5%)	
Pain intensity 6 h			
Mild (NRS 1–3)	117 (32%)	192 (70%)	0.000
Moderate (NRS 4–6)	246 (66%)	83 (30%)	
Severe (NRS 7–9)	7 (2%)	–	
Pain intensity 12 h			
No pain (NRS 0)	1 (0.3%)	–	0.000
Mild (NRS 1–3)	300 (81%)	260 (94.5%)	
Moderate (NRS 4–6)	69 (18.7%)	15 (5.5%)	
Pain intensity 24 h			
No pain (NRS 0)	88 (24%)	86 (31%)	0.034
Mild (NRS 1–3)	282 (76%)	189 (69%)	
Additional analgesics n (%)	60 (16.2%)	19 (6.9%)	0.000
Analgesic dosage (mg)	66.6 ± 23.7	52.6 ± 11.4	0.01

NRS numeric rating scale

Table 3 Postoperative nausea and vomiting presenting in female and male patients

	Women (n = 370)	Men (n = 275)	p value
PONV			
Nausea 1 h (n/%)	65 (17.6%)	28 (10.2%)	0.008
Nausea 6 h	39 (10.5%)	13 (4.7%)	0.007
Nausea 12 h	12 (3.2%)	4 (1.5%)	0.15
Nausea 24 h	4 (1.1%)	1 (0.4%)	0.30
Vomiting 1 h (n/%)	36 (9.7%)	11 (4%)	0.006
Vomiting 6 h	14 (3.8%)	3 (1.1%)	0.03
Vomiting 12 h	1 (0.26%)	2 (0.7%)	0.4
Vomiting 24 h	0	0	NC
Additional antiemetics (n/%)	35 (9.5%)	11(4%)	0.008
Antiemetic dosage (mg)	9 ± 4	5.8 ± 2.7	0.016

PONV postoperative nausea and vomiting, *NC* not calculable

Hussain et al. [13] evaluated the effect of gender on pain perception and analgesic consumption in postcholecystectomy patients. They recruited 60 female and 60 male patients aged 20 to 60 years scheduled for LC. The authors reported that women presented with higher levels of pain according to the NRS scale in the immediate postoperative period (20 to 30 min after surgery). Female patients required higher dosages of narcotic analgesics as respite from pain. Subsequent serial evaluations at 4, 8 and 12 h failed to demonstrate differences. The incidence of PONV

was higher in women (18.3%) than in men (10%), but the difference was not significant, probably because of an insufficient sample size.

In contrast, Theodoraki and his group conducted a study comparing the incidence of pain assessed using VAS in patients after major surgery on the large bowel (right or left colectomy, sigmoidectomy, lower anterior resection and abdominoperineal resection) in patients of both genders with ASA II and III in a total population of 30 women and 30 men. Women presented with lower VAS scores for pain than men, but no difference was found regarding the need for rescue opioids. PONV incidence was similar between groups [14].

In 2014, Tighe et al. [25] published a review of more than 330,000 patient records evaluating the prevalence of pain using the NRS on the first postoperative day after a wide range of surgical procedures. Women reported more postoperative pain (odds ratio 1.16, 95% confidence interval 1.11–1.20). A subanalysis, including 699 cholecystectomy patients of whom 392 were women and 307 were men, showed that the pain intensity was similar (4.9 ± 3.4 and 4.9 ± 3.4, $p = 0.9871$). Severe pain (NRS 7–10) was also similar, presenting in 32% and 29% of women and men, respectively, during the first postoperative day ($p = 0.35$) [25].

Peryasamy et al. [26] studied 231 male and 219 female patients between 18 and 65 years old who underwent elective intraabdominal surgeries under general anesthesia and in whom they evaluated pain and the requirement for additional morphine for its control. Surgical procedures were divided into supra- and inframesocolic. Pain intensity measured with a VAS was higher in women, but the consumption of additional doses of morphine was higher in men than women (34.35 ± 6.68 mg vs. 26.78 ± 7.14 mg, $p < 0.001$). The authors concluded that men required a greater quantity of narcotics; however, this study lacked clarity in its design and specific procedures [26].

Shin et al. [27] appraised the administration of fentanyl in 731 men and 1096 women. The authors did not describe the laparoscopic procedures to which these patients were subjected. However, they did not find significant differences between genders in the amount of the drug used for pain control.

Most recently, Lee and colleagues performed a clinical trial assessing the efficacy of dexamethasone for postoperative analgesia and prevention of PONV after LC [19]. A total of 196 men and 196 women with an age range of 18 to 45 years were included. The general incidence of PONV was 23.8% and 48% in men and women, respectively ($p < 0.05$). In the dexamethasone group, the incidences were 16.0% and 31.6% respectively ($p < 0.05$). The authors concluded that women have higher VAS scores 1 h and 6 h after surgery, with a tendency to equalize at 12 h and 24 h.

With a similar purpose, Chae and his colleagues conducted a trial to evaluate gender-related differences in postoperative pain after LC [28]. They recruited 106 women and 103 men. To assess pain, they used the NRS scale. In the immediate postoperative period women had higher scores for pain (NRS 5–7) than men (NRS 4–6, $p = 0.001$). However, in subsequent evaluations, pain levels were similar between genders at 8, 16 and 24 h postoperatively.

Our study has several limitations. The first is related to the methodological design because this was not a prospective controlled trial. However, the cohort design supports the reliability of our findings that pain and PONV were more common in women, particularly young women. Although the purpose of this study was to identify differences between men and women, we observed that older women required fewer doses of narcotics than younger women. These findings will require a new study comparing pre- and postmenopausal women. Because of the standardization of the anesthetic and surgical techniques and postoperative care protocols our findings may offer different conclusions to those of other centers that use different protocols. Because minimally invasive techniques are becoming less and less invasive, we are unable to generalize our results to other laparoscopic techniques.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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