Surg Endosc (2006) 20: 448–451
DOI: 10.1007/s00464-005-0406-0

SURGICAL ENDOSCOPY
and Other Interventional Techniques

Gender differences in postoperative pain after laparoscopic cholecystectomy

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Received: 6 June 2005/Accepted: 2 October 2005/Online publication: 21 January 2006

Abstract
Background: Some evidence suggests that females have a lower pain threshold and a lower tolerance to painful stimuli. This study investigated gender differences in postoperative pain after laparoscopic cholecystectomy (LC) on the basis of visual analog pain scale (VAS) scores and the clinical course.
Methods: The 100 patients in this study (46 males and 54 females) underwent LC for cholecystolithiasis or gallbladder polyps without intraoperative complications. An 8-mm Penrose drain was retained for 42 h below the liver bed. All the patients were hospitalized for 4 days after LC, and the pain reported by patients, the time course of changes in the highest body temperature, the leukocyte count, and the C-reactive protein level were studied comparatively for the male and female patients.
Results: The VAS scores were significantly higher for the female patients than for the male patients at 24 h (62.7 ± 24.6 vs 47.0 ± 23.3; $p = 0.0015$) and at 48 h (39.2 ± 24.3 vs 28.3 ± 19.1; $p = 0.0137$) after LC. The female patients used analgesics more frequently and had significantly higher body temperatures than the male patients on day 1 (37.2 ± 0.6 vs 36.9 ± 0.4; $p = 0.0037$) and day 2 (36.9 ± 0.6 vs 36.6 ± 0.4; $p = 0.0037$) after surgery.
Conclusion: Early postoperative pain after LC was more severe in female patients, and patients with high VAS scores tended to use analgesics more frequently.

Key words: Gender difference — Laparoscopic cholecystectomy — Postoperative pain — Visual analogue scale (VAS) score

Laparoscopic cholecystectomy (LC), currently the standard treatment for cholecystolithiasis and gallbladder polyps, has been used to treat more than 80% of the cholecystolithiasis cases in Japan [20]. Despite its low invasiveness, many patients complain of shoulder tip pain as well as nausea and vomiting postoperatively.

At the Wakayama Medical University Hospital, 1,341 patients have been treated with LC from January 1991 through March 2005, and we are considering a transition to 1-day surgery. To realize this transition, efforts should be made to reduce postoperative pain. Intraoperative high-pressure pneumoperitoneum (> 12 mmHg) [17] stimulation by the carbon dioxide gas used [22] and by the right subphrenic accumulation of gas [10] have been suggested as possible causes of these complications.

Under experimental pain conditions involving mechanical or thermal stimuli, females have demonstrated a lower pain threshold and a lower tolerance of pain than males [5, 6, 12]. Nevertheless, these gender differences in pain perception are not unequivocal. Studies of chronic and experimental pain show a greater prevalence of pain in females than in males, but there is little evidence for gender differences in postoperative pain [8]. A few trials have documented a higher incidence and severity of postoperative pain in females [13]. However, no studies have investigated gender differences in postoperative pain after LC.

In the current study, the time course of changes in postoperative pain, as assessed using the visual analog pain scale (VAS) score reported by patients, and the changes in maximum body temperature, leukocyte count, and level of C-reactive protein were compared between male and female patients.

Patients and methods

This study prospectively enrolled 100 consecutive patients (46 males and 54 females) with cholecystolithiasis or gallbladder polyps who were treated with LC from June 2003 through March 2005. The eligibility criteria required that the study subjects be younger than 80 years, and that they consent in writing to participate in this study. Patients with severe cholecystitis and choledocholithiasis were excluded, as well as patients with a history of upper laparotomy and

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Table 1. Operative findings

	Male (n = 46)	Female (n = 54)
Age (years old)	58.0 ± 14.2	53.1 ± 15.1
Intraoperative blood loss (ml)	34.5 ± 13.4	33.5 ± 12.3
Volume of saline for intraoperative lavage (ml)	464 ± 248	453 ± 228
Intraoperative gallbladder perforation or bile spillage	5	6
Operation duration (min)	90.5 ± 25.3	82.1 ± 18.6
Histological severity of cholecystitis (mild: moderate: sever)	37:10:3	36:12:2
Postoperative bile leakage	0	0
Postoperative complications	0	0
Postoperative hospitalization (days)	4	4
Mortality	0	0

(Mean ± SD)

Table 2. Time course of changes in VAS scores

	Male (n = 46)	Female (n = 54)
Post op. 6 hrs	59.2 ± 29.1	65.4 ± 28.9
Post op. 24 hrs	47.0 ± 23.3*	62.7 ± 24.6
Post op. 48 hrs (6 hrs after drain extubation)	28.3 ± 19.1**	39.2 ± 24.3
Post op. 72 hrs	15.5 ± 17.4	22.0 ± 19.2
Post op. 96 hrs (day of discharge)	9.4 ± 15.1	11.5 ± 12.3

* p = 0.0015 vs. Female (mean ± SD)
** p = 0.0137 vs. Female

those with severe complications, including cardiac, renal, pulmonary disease, and a hemorrhagic tendency attributable to cirrhosis.

In all cases, a Penrose drain 8 mm diameter was inserted below the liver bed after intraperitoneal lavage in patients who had no serious intraoperative complications such as an infective biliary leak or bleeding (> 100 ml). The drain was removed 42 h after the operation. Patients were allocated to each gender group after completion of LC according to an allocation table. Surgery was performed by two experienced laparoscopic surgeons (K.U. and M.T.), each of whom had 15 years of experience with LC.

Using a conventional four-port method [20], the LC techniques were standardized as follows: an umbilical port: 1.5 cm, a port below the xyphoid: 1 cm, 2 ports below the costal arch: 0.5 cm with pneumoperitoneal pressure: 8 mmHg. Drainage was accomplished with Penrose drain tubes 8 mm in diameter. The antibiotics sodium sulbactam and sodium cefoperazone, which show good biliary transfer, were administered to all the patients a total of three times [5]: 30 min before the operation, 4 h after the operation, and the day after the operation.

The intraoperative variables observed were the volume of blood loss, the volume of physiologic saline used for lavage, and the severity of cholecystitis. These variables were classified as mild, moderate, or severe on the basis of postoperative histodiagnosis by an independent pathologist. The postoperative variables were the red blood cell count (RBC), white blood cell (WBC) count and differentiated WBC count, platelet count, and hemoglobin concentration. The levels of transaminase, total bilirubin, total protein, albumin, and C-reactive protein were measured before the operation and on days 1 and 3 after the operation. Changes in maximum body temperature were recorded for four consecutive postoperative days. Postoperative pain was evaluated 6, 24, 48, 72, and 96 h after the operation using the VAS [18], on which each patient indicated the severity of pain using a linear scale from 0 (no pain) to 10 (strongest conceivable pain). The postoperative use of analgesics was not abnormally restricted. An indomethacin suppository (50 mg) was prescribed initially, and if ineffective, pentazocine (15 mg) and hydroxyzine hydrochloride (25 mg) were injected together intramuscularly at the request of the patient.

Data are presented as mean ± standard deviation. For statistical analyses, the Mann–Whitney U test was used to evaluate the differences between male and female patients. Postoperative analgesic data were compared using an χ^2 test as appropriate. Differences with a p value less than 0.05 were regarded as statistically significant.

Results

The intraoperative and postoperative findings from the 100 patients are shown in Table 1. There were no significant differences between the two groups in terms of age, intraoperative blood loss, volume of physiologic saline used for lavage, operation time, or histologic severity of cholecystitis. None of the patients had infection or multiple organ complications postoperatively, and the duration of hospitalization was 4 days for all the patients.

The time course of changes in postoperative VAS scores is shown in Table 2. The VAS scores were significantly and consistently higher for female patients than for male patients: 62.7 ± 24.6 for females versus 47.0 ± 23.3 for males (p = 0.0015) 24 h after the operation, and 39.2 ± 24.3 versus 28.3 ± 19.1 (p = 0.0137) 48 h after the operation. No intergroup differences in VAS scores were observed 72 and 96 h after the operation.

The number of patients who used analgesics postoperatively was compared between the male and female patients (Table 3). Analgesic suppositories (indomethacin, 50 mg) were used by 15 female patients and 5 male patients (p = 0.0449) the day after the operation. Thus, indomethacin suppositories were more frequently used by female patients. The time course of changes in the WBC count from preoperative (baseline) values are shown in Table 4. No intergroup difference was observed on any day. Similarly, no intergroup difference was observed for the time course of changes in C-reactive protein levels (Table 5). Although there was no intergroup difference on the day of operation, significantly higher body temperatures were observed for female

Table 3. Number of patients receiving postoperative analgesics

	Day of op.	Day 1	Day 2	Day 3	Day 4
Analgesic suppository use					
Male: (n = 46)	14	5*	0	0	0
Female: (n = 54)	19	15	0	0	0
Analgesic intramuscular injection					
Male: (n = 46)	4	2	0	0	0
Female: (n = 54)	7	3	0	0	0

* p = 0.0449 vs. Female

Table 4. Time course of changes in WBC count

	Male (n = 50)	Female (n = 50)
Before operation	6,183 ± 2,071	5,626 ± 1,495
Day 1 after op.	8,376 ± 2,142	8,247 ± 2,627
Day 3 after op.	6,578 ± 1,663	6,606 ± 2,064

(Mean ± SD)

Table 5. Time course of changes in CRP level

	Male (n = 50)	Female (n = 50)
Before operation	0.80 ± 1.54	0.28 ± 0.58
Day 1 after op.	2.30 ± 1.72	2.14 ± 3.07
Day 3 after op.	2.11 ± 1.93	3.08 ± 4.71

(Mean ± SD)

patients on day 1 (37.2 ± 0.6°C for female patients vs 36.9 ± 0.4°C for male patients; p = 0.0037) and day 2 after the operation (36.9 ± 0.6°C for female patients vs 36.6 ± 0.4°C for male patients; p = 0.0037).

Discussion

Cholecystolithiasis and gallbladder polyps have been treated conventionally with laparotomy [19]. In contrast to laparotomy, LC has progressed dramatically in the past decade. As a result, hospitalization has shortened, and a quick recovery has become possible because of the small operative wounds and mild postoperative pain. However, the shoulder tip pain, back pain, and nausea/vomiting resulting from pneumoperitoneum, and not experienced with conventional laparotomy, are disadvantages of laparoscopic cholecystectomy [10, 17, 21, 22].

The current trial design allowed us to study the natural course of pain after laparoscopic surgery until analgesia was required. The incidence and severity of early postoperative pain after LC were generally low, but those of moderate-to-severe pain were markedly higher, particularly for the female patients. Some reports have suggested that females may have a lower pain threshold and less tolerance of painful stimuli than males [5, 6, 12]. The lower pain threshold of females may be supported by the finding that more females than males reported severe baseline pain in our study. Sex differences in pain perception have been attributed to a different socialization process for men and women, which influences bodily experience and the willingness to communicate distress [3]. Hormone variations also could help to explain sex differences in pain experience and response to analgesics [4]. Gender differences in analgesic effects also have been demonstrated [13], but these differences cannot explain the differences in postoperative pain because our observation time exceeded the expected duration of the analgesic used. However, the higher pain intensity in women was observed despite the fact that female patients received a larger dose of analgesics.

We found that body temperature usually rose during periods of strong pain. Body temperature is known to rise when strong pain is felt [9], and this supports the rise in VAS score observed in the current study. Postoperative pain, a stressor in both humans and animals, has been previously reported to alter several molecular/biochemical stress markers including adrenocorticotropic hormone (ACTH) [1], corticosteroids [11], ornithine decarboxylase [14], and core body temperature [2].

In the current study, female patients felt stronger pain than male patients, and the body temperature rose only in female patients during that period. Although this is an objective finding, pain is a subjective sensation, which makes comparison difficult. The absence of sex difference in pain sensation has been reported for rats [7], whereas stronger pain responses in females than males have been reported for human subjects [16]. Findings have shown this tendency to be markedly stronger in young female subjects [8], suggesting a higher sensitivity to pain in females. The analgesic effects of scents and music also are stronger in females [15]. From the current study, we postulate that females are more sensitive to strong pain and show a greater range of pain sensation.

In conclusion, we have found clinical evidence that women exhibit higher pain intensity after LC and have larger adjusted analgesic requirements than men, and that patients with high VAS scores tend to require larger doses of analgesics.

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