

ORIGINAL ARTICLES

METABOLIC AND RESPIRATORY CHANGES AFTER CHOLECYSTECTOMY PERFORMED VIA LAPAROTOMY OR LAPAROSCOPY

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SUMMARY

We have compared metabolic and respiratory changes after laparoscopic cholecystectomy ($n = 15$) with those after open cholecystectomy ($n = 15$). The durations of postoperative i.v. therapy, fasting and hospital stay were significantly shorter in the laparoscopy group. During the first and second days after operation, analgesic consumption but not pain scores (visual analogue scale) were significantly smaller after laparoscopy, while vital capacity, forced expiratory volume in 1 s, and Pa_{O_2} were significantly greater. The metabolic and acute phase responses (glucose, leucocytosis, C-reactive protein) were less after laparoscopy compared with laparotomy. Although plasma cortisol and catecholamine concentrations were not significantly different between the two groups, after surgery interleukin-6 concentrations were less in the laparoscopy group.

KEY WORDS

Lung: postoperative function. Metabolism: acute phase reaction. Pain: postoperative. Surgery: cholecystectomy, laparoscopic surgery.

Laparoscopic cholecystectomy is said to have many advantages [1–2] compared with the open operation, the major one being a shorter duration of hospital stay [3]. Upper abdominal surgery is followed by several side effects: pain, pulmonary dysfunction and endocrine and metabolic changes. It is conceivable that the faster recovery and feeling of well-being described after laparoscopic compared with open cholecystectomy might reflect better maintenance of homeostasis. However, no studies have examined this area [4].

We have therefore compared postoperative pain, pulmonary dysfunction and endocrine and metabolic changes after cholecystectomy performed by either laparotomy or laparoscopy.

PATIENTS AND METHODS

We studied 30 patients, ASA grades I and II, undergoing elective cholecystectomy, after local Ethics Committee approval and informed patient consent had been obtained. None of the patients had

acute cholecystitis. Fifteen patients underwent laparoscopic cholecystectomy and the data obtained were compared with those from 15 previously investigated [5] patients who underwent laparotomy via a subcostal incision. All pre-, intra- and post-operative conditions other than the surgical approach (surgeons, anaesthetists, nurses, observers) were similar for the two groups (table I). All operations were performed in the morning after an approximate preoperative fast of 8 h.

All patients were premedicated with hydroxyzine 50–75 mg orally 2 h before surgery and an i.m. injection of midazolam 5 mg and atropine 0.25 mg just before transfer to the operating theatre. Anaesthesia was induced with sufentanil 15–20 µg, thiopentone 5 mg kg⁻¹ and atracurium 0.5 mg kg⁻¹. After tracheal intubation, general anaesthesia was maintained with 50% nitrous oxide in oxygen and isoflurane as needed. The duration of surgery (time elapsed from the end of the induction of anaesthesia until skin closure) and the mean end-tidal concentration of isoflurane (Datex Capnomac) were recorded. During laparoscopic procedures, intra-abdominal pressure was maintained automatically at 14 mm Hg by a carbon dioxide insufflator (Wolf 2154.201). Patients were placed in a 10° head-up position. During surgery, all patients received an i.v. infusion of lactated Ringer's solution. After surgery, a 5% glucose solution was infused at a rate of 80 ml h⁻¹.

Pain assessment

Pain score was assessed using a 100-mm visual analogue scale [6] when patients requested analgesic medication, 4 h after the end of surgery, at 08:00, 14:00 and 20:00 on day 1 and at 08:00 on day 2. Both groups received i.m. injections of piritramide 0.2 mg kg⁻¹ 4 hourly as required and the consumption was recorded during the first 48 h. Patients from both groups received the same information from the

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TABLE 1. Patient characteristics and details of hospital stay (mean (range or SEM)). * $P < 0.05$ between groups

	Laparoscopy ($n = 15$)	Laparotomy ($n = 15$)
Age (yr)	46.0 (22–65)	51.8 (29–70)
Weight (kg)	71.4 (3.7)	74.7 (3.5)
Height (cm)	164.7 (2)	168.0 (2.4)
Sex (F/M)	12/3	9/6
Duration of surgery (min)	121 (10)	96 (11)
Isoflurane (%)	0.86 (0.05)	0.83 (0.07)
Duration of postop. i.v. infusion (h)	20.6 (2.85)	* 40.3 (3.33)
Duration of postop. fasting (h)	16.1 (2.17)	* 29.17 (3.33)
Duration of postop. hospital stay (day)	2.75 (0.16)	* 5.0 (0.25)

same anaesthetist (J.J.) and nurses concerning analgesic availability. Piritramide 20 mg has been shown to be equianalgesic with morphine 15 mg [7].

Pulmonary function

Pulmonary function was measured by the same technician with the patient in a semi-sitting position before surgery, 4 h after the end of surgery and 2 days after surgery, using a Gould Pulmonet III. Patients were kept in this position for 20 min before testing without supplementary oxygen. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), ventilatory frequency (f), tidal volume (V_T) were measured and the greatest value of three attempts was recorded. Arterial blood samples were obtained by femoral artery puncture for blood-gas analysis, just before pulmonary function testing.

Endocrine and metabolic responses

Blood samples were obtained from an antecubital vein before surgery, 4 h after the end of surgery and on days 1 and 2 at 08:00. Plasma concentrations of glucose, C-reactive protein (CRP), cortisol, catecholamines and interleukin-6 (IL-6) and leucocyte counts were measured, by technicians blinded to the type of surgery.

Serum concentration of CRP was measured by laser nephelometry (Behring, Marburg, Germany). The sensitivity of the assay was $2.5 \text{ mg litre}^{-1}$ and intra-assay and interassay coefficients of variation were 2.3% and 10%, respectively.

Plasma concentration of total cortisol was measured by direct radioimmunoassay [8]. The sensitivity of the assay was $25 \text{ nmol litre}^{-1}$. All assays were processed in duplicate with maximal 4.3% intra-assay and 8.3% interassay coefficients of variation.

Plasma concentrations of adrenaline and nor-adrenaline were measured using high-pressure liquid chromatography with electrochemical detection [9]. Sensitivity of these two assays was $0.02 \text{ nmol litre}^{-1}$. Intra- and interassay coefficients of variation were 7.4% and 9.8%, respectively.

IL-6 was measured by a two-step immuno-radiometric assay (IRMA) using a prototype from Medgenix (Fleurus, Belgium) [10]. Briefly, the two-step IRMA is based on coated-tube separation and on an oligoclonal system in which several monoclonal antibodies are directed against distinct epitopes of

IL-6. The captured antibodies are attached to the lower and inner surface of plastic tubes which are provided in the kit. The IL-6 concentration of samples was determined by interpolation using a standard curve prepared at the same time. The sensitivity of this IRMA was 5 pg ml^{-1} . Intra- and interassay variability were 5.6% and 7.5%, respectively. The recovery test showed an 89% recovery. Normal values are $< 10 \text{ pg ml}^{-1}$.

Statistical analysis

Results are reported as mean (SEM). Time-dependent variables in the treatment groups were compared by Zerbe's method [11]. This technique allows one to test the hypothesis of the equality of response curves for two or more groups at each time or during any given time interval. It uses an F -test in which the degrees of freedom depend not only on the group sample sizes, but also on the time period chosen. Student's t test was also used when appropriate. Correlation between CRP and IL-6 concentrations was tested for significance by linear regression. All results were considered to be statistically significant at the 5% level.

RESULTS

Both groups were comparable except for the sex ratio (table I). The duration of surgery for laparoscopy was longer than that for laparotomy (ns: $P = 0.07$) (table I). The mean end-tidal concentration of isoflurane needed to keep the patient haemodynamically stable during surgery was similar with both surgical techniques: approximately 0.85%. In contrast, duration of postoperative i.v. infusion, postoperative fasting and hospital stay were significantly shorter in the laparoscopy group ($P < 0.05$).

Pain and analgesic consumption

Pain reported immediately after surgery was less intense after laparoscopy than after laparotomy (ns: $P = 0.19$) (fig. 1). The duration of pain was shorter in the laparoscopy group (see day 2) and pain scores were more variable in the laparoscopy group. Overall, pain intensity did not differ significantly between the two groups ($P = 0.17$). However, on day 2, pain was negligible after laparoscopy and significantly less than after laparotomy ($P < 0.05$).

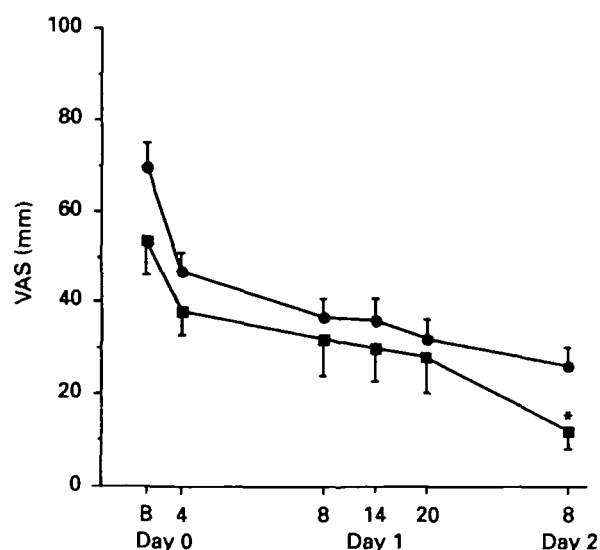


FIG. 1. Pain scores (mean, SEM) after cholecystectomy by laparoscopy (■) and laparotomy (●). Pain was assessed before administration of analgesia (Day 0: B), 4 h after the end of surgery (Day 0: 4) on day 1 at 08:00 (8), 14:00 (14) and 20:00 (20) and on day 2 at 08:00 (8). * $P < 0.05$ between groups.

Although pain was similar in both groups at most time points, a two-fold reduction in analgesic consumption was observed after laparoscopy during the first and second days (first day: piritramide 0.22 (SEM 0.04) mg kg^{-1} vs 0.37 (0.03) mg kg^{-1} ($P < 0.05$); second day: piritramide 0.06 (0.04) mg kg^{-1} vs 0.24 (0.04) mg kg^{-1} ($P < 0.05$)). Whereas four of 15 patients requested analgesic on the second day in the laparoscopy group, 12 of 15 requested it in the laparotomy group. After laparotomy, patients complained more of parietal pain (abdominal wall), whereas after laparoscopy patients reported visceral pain similar in location and type to biliary colic, and shoulder-tip pain secondary to diaphragmatic irritation.

Pulmonary function

After surgery, FVC and FEV₁ decreased in both groups (table II). Tidal volume decreased, but

minute ventilation was unchanged because of a compensatory increase in ventilatory frequency. After laparoscopy, the reductions in FVC and FEV₁ were not as pronounced as after laparotomy ($P < 0.05$). Two days after laparoscopy, patients had a greater Pa_{O_2} than those who had laparotomy ($P < 0.05$).

Endocrine and metabolic responses

Before operation, endocrine and metabolic variables were similar in both groups. In particular, median serum concentrations of IL-6 in the two groups were $< 5 \text{ pg ml}^{-1}$ —the assay detection limit. Serum concentrations of cortisol increased after operation at 4 h and returned to normal values on day 1, with no significant difference between the two groups at any time (fig. 2). Plasma concentrations of catecholamines did not differ significantly between the two groups (fig. 2). IL-6 was released during the postoperative period; at 4 h, the serum concentration was significantly less after laparoscopy ($P < 0.05$) (fig. 2). Plasma concentrations of glucose and CRP, and leucocyte counts increased in both groups after surgery, but the values were significantly smaller and of shorter duration in the laparoscopy group ($P < 0.05$) (fig. 3). There was a linear correlation between the peak concentrations of IL-6 and CRP ($r = 0.64$, $P < 0.05$).

DISCUSSION

Surgery is associated with metabolic and acute phase responses characterized by clinical and biological events: hyperglycaemia, leucocytosis, fever and production of acute phase proteins, such as CRP, by the liver [12]. The acute phase reaction, and more particularly the serum concentration of CRP, reflect the amount of tissue damage [13] and the severity of illness [14]. We have shown that this acute phase reaction was significantly reduced after laparoscopic cholecystectomy than that after laparotomy. The different glycaemic responses of the two groups were not caused solely by the shorter duration of fasting and infusion of 5% glucose in the laparoscopy

TABLE II. Pulmonary function before surgery (Pre.), 4 h after operation (4 h) and on day 2 after cholecystectomy performed via laparoscopy or laparotomy (mean (SEM)). FVC = Forced vital capacity; FEV₁ = forced expiratory volume in 1 s; VT = tidal volume; f = ventilatory frequency. * $P < 0.05$ between groups

	Pre.	4 h	Day 2
FVC (ml)			
Laparoscopy	3073 (173)	2150 (216)	2600 (192)
Laparotomy	3291 (167)	1522 (131)*	1946 (111)*
FEV ₁ (ml s ⁻¹)			
Laparoscopy	2342 (141)	1600 (190)	1992 (150)
Laparotomy	2331 (164)	969 (110)*	1400 (106)*
VT (ml)			
Laparoscopy	615 (30)	429 (23)	500 (30)
Laparotomy	631 (39)	428 (28)	503 (49)
f (b.p.m.)			
Laparoscopy	14 (1)	16 (1)	15 (1)
Laparotomy	14 (1)	16 (1)	14 (1)
Pa_{O_2} (kPa)			
Laparoscopy	12.4 (0.53)	10.5 (0.48)	11.2 (0.55)
Laparotomy	11.8 (0.35)	10.0 (0.27)	10.1 (0.44)*
Pa_{CO_2} (kPa)			
Laparoscopy	4.7 (0.13)	5.0 (0.13)	4.8 (0.16)
Laparotomy	4.8 (0.11)	4.9 (0.16)	5.0 (0.11)

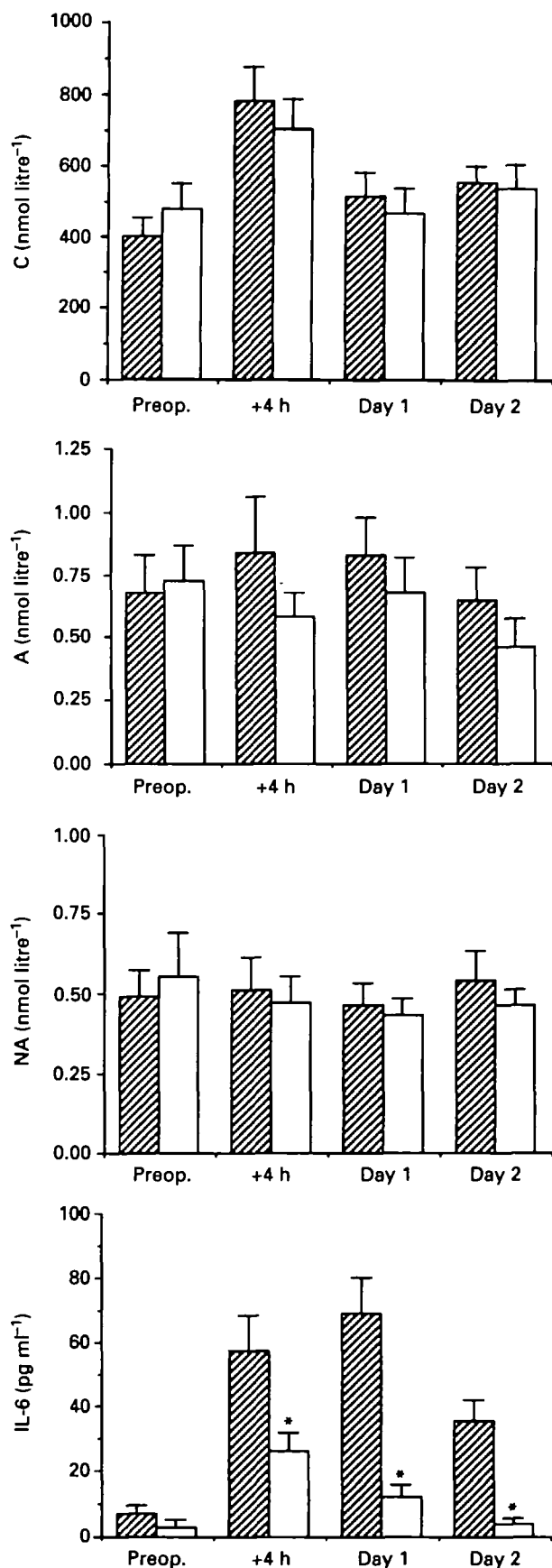


FIG. 2. Neuroendocrine response and interleukin-6 (IL-6) release (mean, SEM) after cholecystectomy by laparotomy (▨) and by laparoscopy (□). Samples were taken before surgery (Preop.), 4 h after surgery (+4 h), and on days 1 and 2 (at 08:00). C = Cortisol; A = adrenaline; NA = noradrenaline. Comparison of the two response curves for IL-6: $F = 18.99$, $P < 0.05$. * $P < 0.05$ between groups.

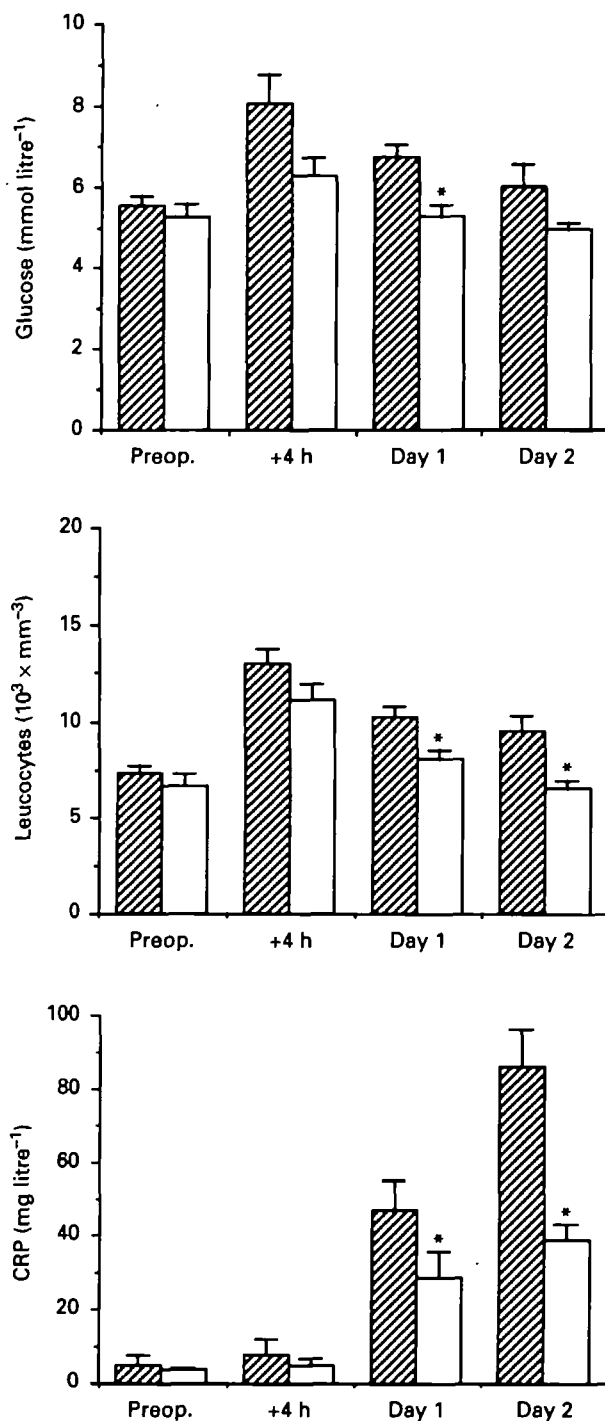


FIG. 3. Metabolic and acute phase responses (mean, SEM) after cholecystectomy by laparotomy (▨) and by laparoscopy (□), measured before surgery (Preop.), 4 h after surgery (+4 h), and on days 1 and 2 (at 08:00). CRP = C-reactive protein. Comparison of the two response curves for glucose: $F = 6.13$, $P < 0.05$; for leucocytes: $F = 5.87$, $P < 0.05$; for CRP: $F = 12.70$, $P < 0.05$. * $P < 0.05$ between groups.

group. Ten of the 15 patients in this group still had an infusion in progress on day 1 at 08:00. Using only these 10 patients, the differences between the two groups at the first three sampling times remained statistically significant ($F = 6.63$; $P < 0.05$).

The metabolic response is mediated by neuroendocrine stimulation in addition to release of inflammatory mediators (cytokines) from the surgical wound [15]. One of these cytokines, interleukin-6, is

activated by tissue trauma, and appears to be the most efficient stimulator of hepatic acute phase protein production [16, 17]. Increases in IL-6 concentrations were significantly smaller after laparoscopy than after laparotomy ($P < 0.05$), and there was good correlation between peak concentrations of IL-6 and CRP. In contrast, the observation that plasma concentrations of cortisol and catecholamines were not significantly different between the two groups suggests that the neuroendocrine stimulation induced by the two surgical procedures was similar. However, overall, our results provide biochemical evidence that the extent of surgical trauma was less for laparoscopy than for open cholecystectomy.

A reduction in surgical trauma has economic and clinical consequences. Postoperative fasting, duration of i.v. infusion and hospital stay were significantly less after laparoscopy than after laparotomy. Surgical trauma contributes to pain and pulmonary dysfunction. After laparoscopic cholecystectomy, pain was not significantly less than after laparotomy except on day 2. However, consumption of opioids to attain similar degrees of analgesia was significantly less after laparoscopy. The duration of pain after laparoscopic cholecystectomy was shorter, as indicated not only by the reduced pain score on day 2, but also by the reduction in requests for opioids.

The postoperative changes in pulmonary function were typical of upper abdominal surgery [18]. Our findings confirm that laparoscopic cholecystectomy results in less respiratory dysfunction than laparotomy [19]. Whereas FVC and FEV₁ differed markedly in the two groups, at both postoperative observation times, differences in PaO₂ were less obvious. The lack of significant difference in relative hypoxaemia measured at 4 h, in spite of a marked difference in pulmonary dysfunction, might be a reflection of sedation secondary to residual effects of anaesthesia and opioids, in addition to pain.

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