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Metabolic and inflammatory responses after laparoscopic and open inguinal hernia repair

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A prospective comparison of metabolic and inflammatory responses after laparoscopic and open inguinal hernia operations was undertaken. There were 10 patients in each group. Plasma levels of cortisol, growth hormone, prolactin, C-reactive protein (CRP) and interleukin-6 (IL-6) were measured preoperatively and at fixed intervals up to 120 h postoperatively. *In vitro*, endotoxin stimulated whole blood tumour necrosis factor alpha (TNFα) was measured in preoperative and 24 h postoperative blood samples. Changes in the plasma levels of cortisol, growth hormone and prolactin showed no statistically significant difference between the groups. No significant change in IL-6 levels were recorded in any group. Changes in CRP levels were significantly higher ($P < 0.006$) in open hernia patients. Endotoxin stimulated TNFα production was suppressed in both groups. The degree of suppression in open hernia patients was significantly higher ($P < 0.005$). This study has shown that both these operations produce similar stress responses. However, open hernia operation results in a higher acute phase response and induces a greater endotoxin tolerance.

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Inguinal hernia repair is one of the most common surgical procedures performed. Following the success of laparoscopic cholecystectomy, there has been a growing interest in applying laparoscopic methods to inguinal hernia repair *(1,2)*. However, laparoscopic hernioplasty does not provide as clear an advantage over its conventional counterpart as laparoscopic cholecystectomy. Considerable doubt remains about the virtue of an operation which appears to be more complicated and has few apparent benefits over the open operation *(3)*. Hence, there is a need for further studies to compare these two procedures of inguinal hernia repair.

Surgical trauma stimulates a series of hormonal, metabolic and inflammatory changes *(4,5)*. Laparoscopic operations are considered to be minimally invasive and might be expected to produce a lower response compared with the conventional open operations. We have conducted a prospective study to assess the difference between laparoscopic and open inguinal hernia repairs with respect to stress and inflammatory responses.

The hypothalamic–pituitary–adrenal axis is one of the physiological mediators of stress. It is postulated that the hypothalamus controls the changes that occur in circulating hormones as a result of stress, including an increase in the production of human growth hormone, cortisol and prolactin. Previous studies have demonstrated that the levels of various pituitary and adrenal hormones rise after surgical procedure *(6)*. Furthermore,

changes in their levels have frequently been used to compare the stress produced by operations *(7)*. The stress hormones that we measured were cortisol, human growth hormone and prolactin.

Acute phase protein response after surgical trauma is believed to be proportional to the severity of trauma. C-reactive protein (CRP) is the most commonly studied protein of the acute phase response. After surgical procedures there is usually an increase in CRP levels and changes have repeatedly been shown to reflect the severity of the surgical procedure *(8,9)*. Interleukin-6 (IL-6) is one of the mediators of the acute phase response. It has been shown that plasma IL-6 levels rise after surgery. This rise reaches its peak between 6 and 12 h after operation. It has been shown to be proportional to the severity of surgical injury and is considered to be a sensitive indicator of surgical trauma *(10,11)*. In this study we have measured CRP and IL-6 levels to compare the acute phase protein response after laparoscopic and open hernia operations.

TNFα plays a significant role in immune and inflammatory responses in the body. This cytokine is produced mainly by the macrophages and monocytes. The regulation of macrophage cytokine release is complex and remains incompletely understood. Endotoxin tolerance is a potential control mechanism initially described as an *in vivo* phenomenon whereby a sublethal injection of lipopolysaccharide (LPS) abrogated the response to a subsequent endotoxin exposure *(12)*. This tolerance has been reproduced in multiple animal and human models *(13,14)*. The downregulation of the cytokine response has also been observed in sepsis *(15)* and after surgery *(16)*. We have measured *in vitro* endotoxin stimulated TNFα production after hernia operations to compare the effect of these two operations in its regulation.

Patients and methods

After receiving local ethical committee approval and written informed consent, 20 patients were enrolled from the elective admissions for inguinal hernia repair. Ten patients underwent an open operation while the remainder had their inguinal hernia repair performed laparoscopically. Patient selection was not randomised. The patients were drawn from the waiting list of two different surgical teams, one of which offered a laparoscopic procedure for all the inguinal hernia operations. No patient suffered from any chronic systemic illness or was taking any long-term medication. Patients with diabetes mellitus, obesity, cardiac or respiratory failure, or those with inguinoscrotal or recurrent hernias were excluded from the study. Anaesthetic and operations were standardised as far as possible to minimise interpatient variation.

Anaesthetic technique

After 6–8 h of fasting, anaesthesia was induced using thiopentone or propofol and was maintained with a mixture of 70% nitrous oxide in oxygen supplemented with isoflurane or enflurane. Neuromuscular blockade was achieved with pancuronium or atricarium and was reversed with neostigmine.

Open operation

Open hernia operations were performed through an oblique inguinal incision. All repairs employed a modified Shouldice technique in which the posterior wall was repaired in two layers. The fascia transversalis was double breasted and the conjoint tendon was approximated to the inguinal ligament using nylon sutures.

Laparoscopic operation

Laparoscopic repair was performed by a three port entry into the peritoneal cavity. Pneumoperitoneum was first established. Ports were sited through the umbilicus and in each iliac fossa. Peritoneum was opened in the groin with reduction of the sac. A 13×9 cm prolene mesh was placed extraperitoneally and secured in position by multiple staples. Peritoneum was closed over the mesh.

Postoperative analgesia

Neither group received local or regional anaesthesia and postoperative pain relief relied on intramuscular pethidine and/or oral paracetamol.

Postoperative pain was recorded using a visual analogue scale of 0 to 10, where 0 was no pain and 10 was the worst possible pain.

Experimental protocol

A 15 ml blood sample was collected from a peripheral vein in a heparinised tube before surgery and at 3, 6, 12, 24, 48, 72 and 120 h after operation. After discharge from the hospital, blood samples were collected by visiting patients at their home. Blood samples were centrifuged within 1 h. Plasma was isolated, aliquoted and stored at −20°C. Subsequent estimation of plasma levels of cortisol, growth hormone, prolactin, C-reactive protein (CRP) and interleukin-6 (IL-6) were undertaken as described below.

A further 5 ml of whole blood was collected separately at two time points preoperatively and at 24 h postoperatively in a bottle containing lithium-free heparin. This was used for *in vitro* estimation of endotoxin stimulated production of TNFα. Each sample was divided into two, one of which was stimulated with endotoxin (5 endotoxin units per ml, Quadratech, Epsom, UK) while the other served as a control. Both samples were incubated for 4 h at 37°C and then spun at 800*g* for 10 min. The plasma was separated, aliquoted and frozen at −20°C. TNFα levels were estimated in batches using the method described below.

Biochemical assays

Cortisol was measured by a competitive radioimmunoassay with a radioiodine labelled tracer and polyethylene glycol separation. Growth hormone was measured using an inhouse two-site immunoradiometric assay. Results are reported in mμ/l of the standard 80/505 from the National Institute of Biological Standards and Control (NIBS), Potter's Bar, UK. Prolactin was measured on a Wallac/LKB AuotoDelfia® automated immunoassay analyser. Results are reported in mμ/l of standard 84/500. CRP was measured by rate nephelometry on a Beckman Array 360 analyser. The inter- and intra-assay c.v. for these assays was < 10% and they were controlled in the appropriate national quality assessment schemes (UK).

TNFα *(17)* and IL-6 *(18)* were measured using two-site labelled antibody assays with monoclonal capture antibody and polyclonal detection antibody. A peroxidase labelled tertiary antibody measured with a chemiluminescent substrate was used for quantitation. Both assays were calibrated against NIBS standards and the sensitivities were < 32 pg/ml with interassay c.v. of < 12%.

Statistical analysis

Statistical analysis was performed with the Statistical Package of the Social Sciences (SPSS, Chicago, Illinois, USA) software. The repeated measure analysis of variance was used to compare behaviour of the two groups over the timepoints. The non-parametric Mann–Whitney *U* test was used to compare the groups at the different timepoints. A value of $P < 0.05$ was regarded as significant.

Results

The mean age of the laparoscopic group was 56 years (range 26–70 years), while that in the open hernia group was 48 years (range 22–64 years). This difference in age between the groups was not statistically significant. There was one female in the laparoscopic group, all the other patients were male. The mean operative time was 60 min (range 40–90 min) for laparoscopic operations and 45 min (range 30–68 min) for open operations, this difference was statistically significant ($P < 0.03$). There was no statistically significant difference in the hospital stay between the groups (Table I). The median pain score for open hernia patients during the first 24 h after operation was 4.5 while the laparoscopic group score was 3. This difference was statistically significant ($P < 0.001$). Thereafter the pain became minimal with no difference between the groups. Pethidine use was restricted to the first 24 h after operation. The total pethidine used was a median of 100 mg in the laparoscopic group and 200 mg in the open group. This difference was not statistically significant. Paracetamol used was a median of 3500 mg in the laparoscopic group and 4500 mg in the open group; again this difference was not statistically significant.

Table I. Group details

	Laparoscopic hernia	*Open hernia*
No. of patients	10	10
No. male:female	9:01	10:00
No. indirect:direct	7:06	7:05
Operation time (min)	60 (40–90)	45 (30–68)
Hospital stay (h)	32 (20–74)	39 (21–90)

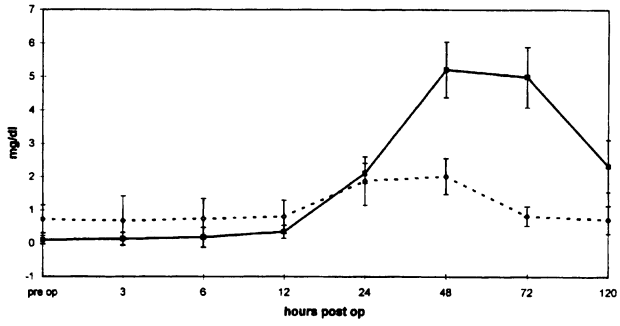

Figure 1. C-reactive protein levels (mg/dl). Mean values in patients undergoing laparoscopic (dotted line) and open (solid line) hernia operations. Significantly higher levels ($P < 0.006$) for open hernia at 48 h.

The plasma cortisol levels peaked at 3 h returning to near preoperative value by 12 h in both groups (Table II). Compared with the preoperative levels, the rise was significant in both groups ($P < 0.03$); however, the difference between the groups remained statistically not significant. Growth hormone rose to a peak in both groups at 3 h and returned to preoperative levels by 12 h. The difference between the groups remained statistically not significant (Table II). Prolactin reached its peak values in both groups at 3 h. There was no statistically significant difference between the groups (Table II). Only five patients (two laparoscopic and three open) showed a rise in their IL-6 levels, in all other patients IL-6 remained undetectable at all timepoints studied. CRP rose significantly in both groups, reaching a peak at 48 h. The peak value was significantly higher in the open group ($P < 0.006$ (Fig. 1). Endotoxin stimulated TNFα levels were measured successfully in nine patients in the laparoscopic group and in eight patients in the open group. Median preoperative TNFα was 795 ng/ml (interquartile range 242–1366) in the laparoscopic group and 1200 ng/ml (interquartile range 530–1476) in the open group. This difference was not statistically significant. Postoperatively, TNFα was reduced significantly at 455 ng/ml (interquartile range 179–984; $P < 0.02$) in the laparoscopic group and also reduced significantly in the open group (248 ng/ml; interquartile range 87–719; $P < 0.02$). However, the median percentage fall in endotoxin stimulated TNFα at 24 h compared with preoperative value was 72% in the laparoscopic group and 34% in the open group. This percentage fall in TNFα was significantly higher in the open group ($P < 0.005$) (Fig. 2).

Table II. Cortisol, growth hormone, and prolactin levels. Before operation and hours postoperatively. Median values with range in brackets

Pre op	3	6	12	24	48	72	124
Cortisol (nmol/l)							
429 (124–743)	702 (159–1397)	571 (379–1101)	456 (247–673)	448 (153–814)	413 (134–523)	424 (317–649)	321 (168–604)
383 (319–480)	811 (337–1131)	600 (242–1050)	485 (74–1038)	470 (156–677)	335 (152–780)	228 (93–571)	302 (107–624)
Growth hormone (mμ/l)							
1 (0.5–8)	1.2 (0.5–25)	1.4 (0.5–5)	2.45 (0.8–9)	0.75 (0.5–4.5)	0.5 (5–2.6)	0.5 (0.5–0.5)	0.5 (0.5–1.1)
0.8 (0.5–2.6)	6.7 (0.5–13.8)	1.7 (0.5–3.9)	1.7 (0.5–1.7)	0.5 (0.5–7.6)	0.5 (0.5–8.8)	0.5 (0.5–1.3)	0.5 (0.5–1.2)
Prolactin (mμ/l)							
154 (88–508)	684 (280–908)	380 (196–503)	231 (160–347)	228 (66–402)	192 (111–380)	190 (94–347)	160 (103–290)
134 (101–620)	554 (272–1290)	319 (199–681)	257 (136–554)	268 (82–415)	230 (96–469)	159 (103–620)	173 (94–626)

LH - Laparoscopic hernia, OH = Open hernia

Figure 2. Percentage fall in TNFα response in 24 h postoperative samples. Preoperative (shaded column) and 24 h postoperative (clear column). Statistically significant difference in TNFα production in 24 h samples ($P < 0.005$).

Discussion

In this study we have measured three different stress hormones namely cortisol, growth hormone and prolactin. The changes in all these three hormones were similar after laparoscopic and open hernia operations. This suggests that the stresses produced by these two different types of hernia operations were similar. The stress that a patient encounters after undergoing a surgical procedure is influenced by multiple factors which include the physical trauma of surgery, the effect of anaesthesia and hospital environment. It is therefore possible that though the stress responses that the patients have shown after laparoscopic and open hernia operation are similar, the surgical trauma produced by these two procedures may still be different.

The CRP levels in both groups showed a characteristic pattern of delayed rise which reached its peak values at 48 h *(19)*. This peak rise was significantly higher in open hernia patients ($P < 0.006$). This result differs from what was observed by Hill *et al. (20)* in their study of changes in CRP levels after laparoscopic mesh hernia repair, open mesh hernia repair and Bassini repair. In their study they found no significant difference in the changes in CRP levels after these procedures. However, in this study the CRP levels were measured only twice at 6 and 24 h after surgery. The changes in CRP levels after injury starts around 12 h and reaches its peak in 48 h and thereafter it gradually declines to normal levels by 5–7 days *(19)*.

Many observers have noted this pattern and it is unlikely that a single measurement at 24 h would give an accurate picture of the change in CRP levels after surgery. A rise in CRP concentration offers the most specific isolated biochemical parameter quantifying the postoperative trauma response. It has been suggested the CRP level can be used to quantify the trauma of surgical operation *(8)*. Higher CRP levels after open hernia operation compared with the laparoscopic procedure suggests that the surgical trauma produced by open inguinal hernia repair may be greater than laparoscopic repair.

There was no significant rise in the IL-6 levels in either the open or laparoscopic group. The peak CRP level in open hernia was 5.2 mg/dl and in laparoscopic hernia 2.4 mg/dl. These values are much lower than those reported in cases of cholecystectomy and other procedures *(6,7)*. To produce a CRP change of this small magnitude, it is possible that the changes in IL-6 levels were minimal and remained below the detection limit of the assay used. Another explanation for this finding of raised CRP levels in the absence of any significant rise in IL-6 value may be that along with IL-6 there are other mediators of acute phase response and they may have been responsible for the rise in CRP levels *(21)*.

The endotoxin stimulated TNF-α levels have shown a wide range of values in pre- and postoperative samples in both laparoscopic and open groups. Compared with the preoperative values, the postoperative levels were significantly lower in both groups. In open hernia repair the TNFα production in response to endotoxin stimulation dropped to 34% of the preoperative value, while in the laparoscopic group the level only fell to 72% of the preoperative value. This shows that laparoscopic hernia repair produces less suppression of TNFα production compared with open procedures. TNFα plays an important part in the body's immune and inflammatory response, a lesser suppression in its production capacity after laparoscopic hernia repair may leave these patients in a better state to combat infections. Studies have shown that in mice, laparotomy results in a decreased capacity of macrophages to present antigen and to express membrane IL-1 activity *(22)*.

Although the materials used for hernia repair in our study were different in laparoscopic and open groups (prolene mesh/nylon sutures) it is unlikely that they could solely be responsible for the difference that we have observed in CRP and endotoxin stimulated TNFα levels between the two groups. We used the Shouldice technique in this study because it was the preferred method of hernia repair for one of the firms involved. Further studies of comparison of laparoscopic and open hernia repair perhaps should involve the use of mesh in both procedures.

Both laparoscopic and open inguinal hernia repairs are surgical procedures of minimal intensity. This study has shown that though the laparoscopic procedure involves entrance to the peritoneal cavity it produces an acute phase response, which is significantly less than that after open operation. The disturbance in the immune system is also less after a laparoscopic procedure. Although the long-term results will be the most important factor in deciding which operation is best, we believe that this study has improved our understanding of the effect of these two procedures on patients.

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