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CLINICAL INVESTIGATIONS

Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses†

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We studied the relationship between the neuroendocrine and inflammatory responses to hip arthroplasty and functional recovery in 102 patients undergoing elective arthroplasty for osteoarthritis. Blood samples were collected for up to 7 days after surgery and analysed for concentrations of norepinephrine, epinephrine, cortisol, interleukin-6 and C-reactive protein. The primary outcome measures were milestones in hospital, times to walk 10 and 25 m, pain on discharge from hospital, and function 1 and 6 months after surgery. Walking distances in hospital were significantly delayed in patients with greater interleukin 6 and C-reactive protein concentrations, but few neuroendocrine measures had significant correlations with functional recovery in hospital. Multivariate analysis showed that the interleukin 6 concentration on day 1 was the unique predictor of time to walk 10 and 25 m, and that the day 2 concentration of C-reactive protein was the unique predictor of pain on discharge from hospital. No significant correlations were found between the inflammatory and neuroendocrine variables and recovery at 1 and 6 months. We conclude that the inflammatory response affects immediate functional recovery after hip arthroplasty.

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Major surgery causes a variety of physiological, subjective and behavioural changes that are known collectively as the 'stress response' to surgery. Many of these physiological responses have been investigated extensively. In particular, neuroendocrine changes have been reported in the anaesthetic literature[1] relating to the effects of anaesthetic techniques, such as regional anaesthesia and high-dose opioid anaesthesia. Nearly 20 yr ago, Kehlet suggested that the neuroendocrine response to surgery was not essential for survival and could even be detrimental, contributing to postoperative complications and delaying recovery.[2] Despite thorough investigation, the hypothesis that decreasing the neuroendocrine changes will enhance recovery is poorly supported. Indeed, one extensive review of regional anaesthesia and postoperative outcome concluded that more studies were needed to determine the relationship between the stress response and postoperative morbidity.[3]

Endoscopic surgery is associated with improved recovery and more rapid discharge from hospital compared with the equivalent open surgical procedure.[4] Neuroendocrine changes are similar for cholecystectomy by laparoscopy compared with laparotomy, but responses, such as those of interleukin 6 (IL-6) and C-reactive protein (CRP), are decreased.[5] We have suggested that the inflammatory response is more important than neuroendocrine changes in determining recovery.[6] The evidence is particularly

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strong for cholecystectomy but less clear for other surgical operations, such as colectomy. Suitable indices of recovery and surgical outcome are hard to define, and for many procedures functional recovery cannot be measured.

We set out to examine the relationship between the neuroendocrine and inflammatory changes and recovery from primary hip arthroplasty undertaken for osteoarthritis. This operation was chosen because it is a common procedure, causes a major physiological response and allows functional recovery to be assessed.

Methods

Patients

After the local Ethics Committee had given approval (GMB/ARM/93/87), patients admitted for unilateral, primary, elective hip arthroplasty for osteoarthritis were studied. Patients admitted before 17.00 h on the day before surgery and scheduled for surgery before 12.00 h were asked to participate. Exclusion criteria included rheumatoid arthritis, major systemic illness likely to alter neuroendocrine and inflammatory changes, such as diabetes mellitus, and steroid medication within the past 6 months. Of 128 suitable patients, 23 declined to participate. Three patients subsequently withdrew from the study so that 102 patients were included.

Anaesthesia and surgery

Patients were premedicated with an oral benzodiazepine before transfer to the operating theatre. On arrival in the anaesthetic room an i.v. cannula was inserted and a blood sample collected. Anaesthesia was induced with thiopentone (n=88) or propofol (n=14) and, after the administration of a non-depolarizing neuromuscular blocking drug, the trachea was intubated and the lungs ventilated with nitrous oxide, oxygen and isoflurane. Intraoperative analgesia was usually provided with i.v. morphine (2.5–28 mg) and occasionally with i.v. fentanyl (50–250 μg). Standard intraoperative monitoring was undertaken and crystalloid solution used for i.v. fluid replacement. Glucose-containing solutions were not given and packed red cells or whole blood were transfused when necessary. In 88 patients a standardized lateral approach was used for a Charnley hip replacement with a trochanteric osteotomy, and the remaining 14 patients had a Monk procedure with an uncemented femoral prosthesis. Postoperative analgesia was provided first by patient-controlled analgesia with morphine and then with oral analgesics—coproxamol, diclofenac or dihydrocodeine.

Procedure

Written informed consent was obtained. On the day before surgery a blood sample was collected, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was determined [7] and a set of psychological questionnaires was administered (not reported here). The WOMAC index measures arthritis-related disability in the hip joint by patients' responses to questions (scored on a five-point Likert scale) about dysfunction, pain and stiffness during routine activities. Responses to several items are added to give separate scores for functional impairment, pain and stiffness, and these are combined to give a total WOMAC score. Patients were also included in a study of the effects of preoperative psychological preparation on postoperative outcome. In brief, patients were assigned randomly to one of three groups: control, relaxation and imagery. None of the variables described here was altered by the differing psychological management.

Blood samples were collected before induction of anaesthesia (0 h), 1, 2, 4, 8, 12 and 24 h after incision, and then daily for 7 days after surgery. Samples of blood were obtained from a cannula in a forearm vein during the first 24 h and subsequently by direct venepuncture.

Analysis of blood samples

Aliquots of plasma and serum were separated from the blood sample within 30 min of collection and stored at –70°C until analysis. Circulating norepinephrine, epinephrine, cortisol, IL-6 and CRP concentrations were measured by methods described in detail previously.[8] Plasma catecholamines were measured for the first 24 h after surgery only and the remaining variables for 7 days.

Physiotherapy regimen

All patients were seen by a physiotherapist on the day after surgery for chest care and circulatory exercises while on bed rest. After a satisfactory radiograph, all patients were expected to leave the bed with assistance on the second day after surgery. Daily walking practice graduated from frame to crutches or sticks and the distance was increased gradually according to the patient's ability. Before discharge from hospital, all patients were able to walk with aids safely and independently and to climb stairs.

Outcome assessment

The primary outcome measures were milestones in hospital, pain on discharge and function at 1 and 6 months. We have shown recently that the times to walk 10 and 25 m with standardized walking aids are a valid assessment of short-term functional recovery after hip arthroplasty and are sensitive to factors known to alter the rate of recovery, such as the age of the patient and different surgical regimens.[9] The physiotherapist's rating of pain on final mobilization was on the following scale: none, a little, moderate, severe. WOMAC questionnaires were completed at a home visit by one of the research team 1 and 6 months after surgery.

Statistical analysis

To normalize the distribution of the data and homogenize variances, all biochemical data were $\log_{10}$-transformed. For multivariate analyses only, missing data were imputed by a maximum likelihood procedure applied to all measurements of each variable in a single block (SPSS 10.0).

Bivariate analyses were undertaken using product-moment correlations. Multivariate analyses were used to confirm and clarify the findings of the bivariate analysis. The days on which the 10 and 25 m walks were achieved were used to indicate functional recovery and multiple regression was used to examine the prediction of each end-point by the biochemical variables. In multivariate analysis each variable was represented by the value of the peak response. The same procedure was applied to the physiotherapist's final assessment of pain.

Statistical analysis was undertaken with SPSS 10.0 and $P<0.05$ was considered statistically significant.

Results

Details of the 102 patients studied are shown in Table 1. The time course of the biochemical variables is shown in Table 2. A significant correlation was found between the duration of surgery and the peak CRP concentration (r=0.23, P=0.02) but not with the peak IL-6 concentration (r=0.19, P=0.051). A detailed description of the endocrine, metabolic and inflammatory responses of 106 patients undergoing primary hip arthroplasty, including the 102 osteoarthritic patients reported here, has been published recently.[8]

There were few postoperative complications: surgical (3), urinary tract infections (3), cardiac (2), respiratory (2), gastrointestinal (2), deep vein thrombosis (1) and other (7).

The mean total WOMAC score decreased from 62 (SEM 1.7) before surgery to 42 (1.6) at 1 month and 27 (2.0) after 6 months. The mean time to walk 10 m was 5 (0.3) days and to walk 25 m was 8 (0.5) days. Mean pain on discharge was 0.28 (0=no pain, 1=little pain).

Prediction of recovery in hospital

No significant correlations were found between preoperative WOMAC and norepinephrine, epinephrine, cortisol and IL-6 concentrations, but a significant correlation was observed with the early CRP response (day –1 to 12 h, $P<0.05$). Walking distances were achieved significantly later in patients with greater IL-6 and CRP concentrations (Fig. 1 and Table 3). This was particularly notable for the CRP results; significant correlations were found for the time to walk both 10 and 25 m from day 3 to day 7 (10 m, $P<0.05$ and $P<0.01$; 25 m, $P<0.05$). Patients with greater CRP concentrations had more severe pain on discharge (8–24 h and days 4 and 5, $P<0.05$; days 2 and 3, $P<0.01$).

There were few statistically significant correlations of functional recovery with the neuroendocrine changes (Table 4) but greater preoperative cortisol concentrations were associated with more rapid recovery and patients with higher norepinephrine concentrations (8, 12 and 24 h) were slower to walk.

Table 1 Details of patients studied. Mean (SD). *Not recorded for one patient; †not recorded for three patients

	Study sample	Withdrew consent	Declined consent
n	102	3	23
Male:female	37:65	3:0	7:16
Age (yr)	69 (29–87)	73*	69 (28–85)
Duration of surgery (min)	110 (29)		
Intravenous fluids (ml)	2110 (686)		
Blood requirement†			
None	37		
1 unit	22		
⩾2 units	40		

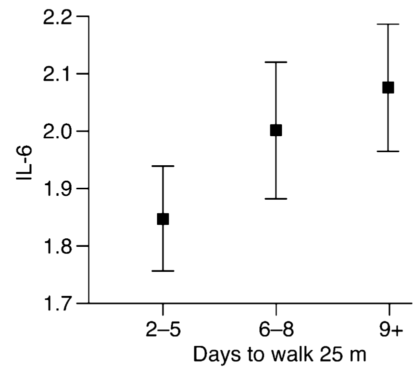

Fig 1 Mean (SEM) $\log_{10}$ IL-6 concentration on day 1 and time to walk 25 m in early (2–5 days), intermediate (6–8 days) and late walkers (⩾9 days). Log 1.7 ≈50 pg ml^{-1} and log 2.3 ≈200 pg ml^{-1} IL-6.

Multivariate analysis

The pattern of these results was confirmed by multiple linear regression analysis. With time to walk 25 m as the response variable, stepwise entry was used (F-to-enter $P<0.05$, F-to-remove $P<0.10$) for the inflammatory and neuroendocrine variables, each represented by the peak response. One variable contributed uniquely: IL-6 on day 1 [β=0.28; b=3.94, 95% confidence interval (CI) 1.25–6.62]. When time to walk 10 m was used as the response variable in a similar analysis, again only IL-6 on day 1 was significant (β=0.22; b=1.78, 95% CI 0.19–3.36). With pain on discharge as the response variable, one predictor was identified: CRP on day 2 (β=0.31; b=0.85, 95% CI 0.33–1.38).

Recovery at 1 and 6 months

No significant correlations were found between the inflammatory and neuroendocrine variables and the 1 and 6 month WOMAC values.

Table 2 Mean (SEM) circulating concentrations of epinephrine, norepinephrine, cortisol, IL-6 and CRP in patients undergoing hip arthroplasty.

	Day –1	Day 0						Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
		0 h	1 h	2 h	4 h	8 h	12 h							
Epinephrine (pmol litre^{-1})	0.53 (0.04)	0.45 (0.03)	0.69 (0.10)	0.97 (0.12)	1.24 (0.16)	0.89 (0.09)	0.62 (0.06)	0.58 (0.08)						
Norepinephrine (pmol litre^{-1})	4.19 (0.21)	3.31 (0.19)	3.79 (0.29)	5.49 (0.33)	6.43 (0.47)	5.41 (0.44)	5.04 (0.39)	4.57 (0.26)						
Cortisol (nmol litre^{-1})	375 (15)	461 (17)	801 (24)	816 (23)	852 (32)	990 (47)	875 (44)	626 (29)	510 (17)	562 (23)	518 (18)	571 (17)	564 (15)	551 (14)
IL-6 (pg ml^{-1})	4.5 (0.9)	5.9 (1.2)	4.9 (0.7)	16.8 (1.4)	72.0 (4.7)	89.2 (8.2)	100.4 (9.5)	129.3 (14.9)	75.8 (8.6)	41.5 (6.4)	27.3 (5.5)	22.0 (2.5)	20.1 (2.4)	18.6 (2.6)
CRP (mg litre^{-1})	8.0 (1.0)	8.0 (1.1)	7.1 (1.3)	7.9 (1.4)	7.5 (1.1)	10.8 (1.4)	28.4 (2.2)	96.1 (4.4)	157.2 (6.3)	154.1 (6.0)	123.0 (5.3)	98.2 (4.8)	79.0 (4.0)	71.5 (4.3)

Table 3 Correlations of circulating concentrations of IL-6 and CRP with functional recovery in hospital. Number of days before patient walked 10 and 25 m and physiotherapist's rating of pain on discharge. *P<0.05; †P<0.01

	Walk 10 m	Walk 25 m	Pain
IL-6 (pg ml^{-1})			
Day –1	–0.05	0.11	0.04
Day 0			
2 h	0.03	0.10	0.10
4 h	–0.05	0.05	0.05
8 h	0.17	0.30†	0.17
12 h	0.15	0.32†	0.17
Day 1	0.23*	0.31†	0.27*
Day 2	0.26*	0.25*	0.17
Day 3	0.18	0.18	0.23*
Day 4	0.16	0.23*	0.15
Day 5	0.18	0.21	0.21
Day 6	0.27*	0.27*	0.11
Day 7	0.17	0.24*	0.14
CRP (mg litre^{-1})			
Day –1	–0.06	0.00	0.03
Day 0			
4 h	–0.13	–0.05	0.16
8 h	–0.14	–0.07	0.24*
12 h	–0.05	0.00	0.24*
Day 1	0.09	0.25*	0.27*
Day 2	0.13	0.23*	0.32†
Day 3	0.25*	0.27*	0.34†
Day 4	0.24*	0.26*	0.27*
Day 5	0.33†	0.28*	0.23*
Day 6	0.29†	0.27*	0.08
Day 7	0.29†	0.25*	0.17

Table 4 Significant correlations of circulating concentrations of norepinephrine, epinephrine and cortisol with functional recovery in hospital. Number of days before patient walked 10 and 25 m and physiotherapist's rating of pain on discharge. Correlations not shown were not significant. *P<0.05

	Walk 10 m	Walk 25 m	Pain
Norepinephrine (pmol litre^{-1})			
Day 0, 8 h	0.24*	0.25*	–0.08
Day 0, 12 h	0.17	0.22*	–0.01
Day 0, 24 h	0.10	0.25*	–0.10
Epinephrine (pmol litre^{-1})			
Day 0, 4 h	–0.23*	–0.11	0.00
Cortisol (nmol litre^{-1})			
Day –1	–0.25*	–0.24*	–0.27*
Day 0, 4 h	–0.21*	–0.08	–0.20
Day 2	0.03	0.23*	0.11

Discussion

We found that the inflammatory response to hip arthroplasty, measured as circulating IL-6 and CRP concentrations, was related to functional recovery. In contrast, the classical neuroendocrine changes—norepinephrine, epinephrine and cortisol concentrations—were relatively unimportant. Furthermore, no relationship was found between the circulating variables measured for up to 7 days after surgery and outcome at 1 and 6 months.

Although the significant correlation coefficients for the inflammatory markers and functional recovery were not high, those for CRP in particular were consistent over several days (Table 3). Subsequent multivariate analysis confirmed the importance of the inflammatory response, as the peak IL-6 value was the unique predictor of time to walk 10 and 25 m and peak CRP predicted pain on discharge. Although perioperative factors, such as haemodilution, red cell transfusion and differing doses of opioids, could affect circulating hormonal and inflammatory variables, small changes in clinical management would have weakened the relationship of the measured variables with recovery. In this descriptive study we chose to reflect clinical practice and did not attempt to control perioperative management. The strengths of the investigation were the large number of patients investigated, the use of one operation for a single pathology, the prolonged sampling schedule and the measurement of functional recovery.

The lack of influence of circulating cortisol, norepinephrine and epinephrine on indices of recovery was in marked contrast to the inflammatory variables (Table 4). The significant negative correlations of cortisol concentrations on the day before surgery with times to walk 10 and 25 m and pain on discharge, were unexpected. It suggests that greater cortisol secretion improves recovery. The mechanism could perhaps be increased anti-inflammatory activity and the mood-enhancing effects of glucocorticoids.[10] It is

notable that this inverse relationship was not found for increased cortisol secretion after surgery except for an isolated significant correlation at 4 h. The influence of preoperative factors was also shown by the correlations between preoperative WOMAC scores and CRP concentrations for the first 12 h after surgery. It is probable that the severity of the osteoarthritis affected the early CRP response before the inflammatory changes induced by surgery became dominant after 12 h. An association between norepinephrine concentrations at 8, 12 and 24 h and times to walk 10 and 25 m was not found for epinephrine. The clinical relevance of these observations is unknown, but it is possible that suppression of adrenergic responses after surgery may confer benefits other than on the myocardium and vasculature.

These results support the hypothesis, deduced from a comparison of cholecystectomy by laparoscopy versus laparotomy, that the inflammatory response is the primary determinant of recovery.[6] Furthermore, this hypothesis can explain why regional anaesthesia, in spite of excellent analgesia, has consistently failed to enhance recovery.[3 11] Although regional anaesthesia may attenuate, and occasionally even abolish, the neuroendocrine response to surgery, the inflammatory changes are not affected.[12 13] The inability of regional anaesthesia to modify the cytokine response to surgery confirms a seminal study in 1980 that found that extensive epidural blockade did not attenuate the acute-phase response to surgery.[14]

At present there are no anaesthetic techniques that have been shown to decrease the inflammatory response consistently. Large doses of the opioid alfentanil, when used as part of a total i.v. technique, suppressed IL-6 secretion transiently.[15] Further studies with low- and high-dose fentanyl failed to confirm these findings.[16 17] Glucocorticoids suppress IL-6 production by an action on cytokine gene expression[18] and a clinical effect has been demonstrated with large doses given before surgery.[19] Unfortunately, the dose needed (methylprednisolone 30 mg kg^{-1}) caused deleterious side-effects (failure of intestinal anastomosis and wound dehiscence) although a later study claimed that no major problems occurred.[20] The important reciprocal interaction between IL-6 and glucocorticoids was shown in a study using etomidate, in which IL-6 release was increased transiently by inhibition of adrenal steroidogenesis.[21]

Non-steroidal anti-inflammatory drugs (NSAIDs) could decrease the inflammatory response to surgery and are widely used. The results are conflicting, although this may reflect the surgical models used and the dose regimens of the NSAIDs.[22–24] A new class of drugs for use in rheumatoid arthritis that not only acts as an NSAID but also inhibits cytokine synthesis offers the possibility of testing the hypothesis directly.[25] At present, decreasing surgical trauma, either by laparoscopy or the use of a smaller incision, is the only way to reduce the inflammatory response.

In conclusion, the notion that the neuroendocrine response to surgery influences recovery is not tenable for primary hip arthroplasty. Instead, attention should be focused on the inflammatory changes that we have shown to be implicated in functional recovery.

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