Circulating levels of interleukin-6 and its soluble receptor in patients with head injury and fracture

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There is evidence that fractures heal more rapidly in patients with head injury. We measured the circulating level of interleukin-6 (IL-6) and its soluble receptor (sIL-6R) and soluble glycoprotein 130 (sgp130) in serum from patients who had sustained a head injury with and without fracture and compared these with levels found in control subjects.

Within 12 hours of injury the serum level of IL-6 was significantly higher in patients with head injury and fracture compared with the control group. Levels of IL-6 were also significantly higher in patients with head injury and fracture compared with fracture only. While there was no significant difference in circulating levels of sIL-6R in the initial samples they were increased one week after surgery in patients with head injury and fracture and with head injury only. In addition, reduced levels of sgp130 in patients with head injury with and without fracture indicated a possible reduction of the inhibitory effect of this protein on the activity of IL-6.

Our study suggests that IL-6 may be involved in altered healing of a fracture after head injury.

The healing of fractures of long bones involves a complex series of cellular and biochemical events which are thought to arise primarily from the response of periosteal cells to disruption of the mechanical integrity of bone.¹ While there have been several reports which indicate that both the production of callus and rates of healing of fractures are increased by concomitant head injury,²⁻⁴ the mechanisms remain unclear. Additionally, heterotopic ossification is found in patients with traumatic paraplegia.³⁻⁵ Either a neuronal or a humoral mechanism might be responsible for the connection between injury to the central nervous system and the formation of new bone at a distant site. Preliminary studies have shown that sera from patients with head injury stimulated both the proliferation of osteoblasts and the production of alkaline phosphatase *in vitro*.^{6,7} If this stimulation is being produced by the same factor or factors responsible for modified healing of the fracture it is important that they are identified.

Interleukin-6 (IL-6) is a pleiotropic cytokine expressed and secreted by cells of the osteoblastic lineage and osteoclasts, among others, in response to osteotropic hormones such as parathyroid hormone, and vitamin D and IL-8.⁸ While the osteoclast is the most abundant cellular source of IL-6 described to

date, IL-6 is a fairly weak stimulator of the formation of osteoclasts *in vitro*.^{9,10} A recent IL-6 knockout model showed increased bone resorption in IL-6 deficient animals which correlated with increased numbers of osteoclasts and suggested that endogenous expression of IL-6 has significant anti-inflammatory effects in modulating the destruction of bone *in vivo*.¹¹ IL-6 exerts its activity via membrane-bound receptors resulting in the homodimerisation of membrane-bound glycoprotein 130 (gp130), and intracellular signalling through tyrosine kinases and phosphorylation.^{12,13} IL-6 receptors are found on osteoblasts^{14,15} and other cell types. A soluble form of the receptor is thought to arise through both proteolytic processing¹⁶ and differential mRNA splicing.^{17,18} Recent literature suggests that the important factors determining biological activity are the concentrations of IL-6/sIL-6R complexes and of free IL-6. The IL-6/sIL-6R complex is able to bind to membrane-bound gp130 and a high plasma concentration of IL-6/sIL-6R will lead to cellular activation *in vivo*. Free IL-6 is able to attach to cells expressing membrane IL-6R and thus yield a more restricted pattern of activation. Similar to IL-6R, differential splicing and proteolytic cleavage result in a soluble form of gp130 (sgp130) which can reduce signalling

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Table I. Details of the patients in the various groups

Case	Age (yrs)	Gender	Patient details*
Head injury and fracture			
1	54	M	GCS 12, ISS 17, haemorrhage, # skull and ribs
2	69	M	GCS 10, ISS 10, haemorrhage, # ribs and pelvis
3	20	F	GCS 10, ISS 18, subdural bleeding, # skull
4	54	M	GCS 6, ISS 40, diffuse HI, # ribs, tibia, fibula and clavicle
5	19	M	GCS 6, ISS 22, closed HI, # clavicle and spine
6	26	F	GCS 3, ISS 34, diffuse HI, # skull and femur
7	28	M	GCS 7, ISS 43, diffuse HI, # skull and ribs
8	19	M	GCS 9, ISS 16, haemorrhage, # skull
9	20	M	GCS 3, ISS 34, frontal contusions and haemorrhage, # clavicle, femur and metacarpals
10	58	M	GCS 7, ISS 11, haemorrhage, # skull and ribs
11	22	F	GCS 8, ISS 9, frontal contusions and haemorrhage, # clavicle
12	18	M	GCS 6, ISS 34, diffuse HI, # skull, clavicle
13	47	F	GCS 7, ISS 20, diffuse HI, # clavicle and femur
14	23	M	GCS 6, ISS 23, assault, closed HI, # ribs
15	18	F	GCS 7, ISS 25, diffuse HI, # skull and ribs
16	23	M	GCS 3, ISS 38, diffuse HI, # skull and ribs
17	26	M	GCS 10, ISS 49, subdural bleeding, # skull and femur
18	53	F	GCS 9, ISS 13, subdural bleeding, # skull
19	21	M	GCS 7, ISS 25, diffuse HI, # skull
20	39	M	GCS 3, ISS 25, haemorrhage, # skull, ribs, and pelvis
21	61	M	GCS 8, ISS 9, haemorrhage, # clavicle
Head injury only			
22	55	M	GCS 7, ISS 15, unrousable because of alcohol
23	25	M	GCS 7, ISS 11, haematoma, frontal contusions
24	36	M	GCS 9, ISS 17, fell downstairs because of alcohol
25	57	F	GCS 3, ISS 25, haematoma
26	26	M	GCS 7, ISS 25, unrousable because of alcohol
27	53	M	GCS 8, ISS 9, unrousable because of alcohol
28	19	M	GCS 6, ISS 25, haematoma
29	42	F	GCS 7, ISS 25, fell downstairs because of alcohol
30	38	M	GCS 4, ISS 25, haematoma
31	68	F	GCS 8, ISS 17, haematoma

* GCS, Glasgow coma score at intubation; ISS, injury severity score; HI, head injury; #, fracture

of IL-6 by inactivating the extracellular IL-6/sIL-6R complex.¹²

We chose to measure the circulating levels of IL-6, sIL-6R and sgp130 in serum because of the known involvement of IL-6 in bone turnover, its role in the pathogenesis of such disease processes in bone as Paget's disease,¹⁹ and the reported elevated level in the plasma of patients with head injury.²⁰ Additionally, animal studies²¹⁻²⁸ and preliminary studies in man^{20,29-31} have shown increased levels of IL-6 after trauma, but the possible effect on the repair of fractures and measurement of sIL-6R and sgp130 in the same patients have not been reported. To date, there have been few studies of human subjects with head injuries and none which have examined specifically IL-6, sIL-6R or sgp130 in patients with both head injuries and fractures.

Patients and Methods

Patients were selected based on the following exclusion criteria: younger than 18 years of age, over the age of 75 years, diabetic, receiving steroids or bisphosphonates and with a previous head injury or bone related pathology. Details of the patients with head injury and fracture and head injury alone are given in Table I. In addition there were 13 patients

with fracture only. There were six women and seven men with a mean age of 38.7 (21 to 73) whose fractures involved the femur (seven), upper limb (two), tibia and fibula (one), ankle (one), arm and foot (one) and spine (one).

The Glasgow coma scale (GCS) and injury severity score (ISS) were calculated for each patient with a head injury both on arrival and at intubation. All procedures were performed under the guidelines of and following approval from the local research ethics committee. Within the first few hours of admission to hospital 20 ml of blood were obtained from 21 patients with head injury and fracture, ten with head injury only and 13 with fracture only. Weekly blood samples were obtained from those with a head injury for the duration for their stay in hospital which varied from between one and three weeks. Blood was also taken from 13 patients attending outpatient appointments (phlebotomy controls following the same exclusion criteria); there were four women and nine men with a mean age of 34.1 years (18 to 67) and from ten apparently healthy volunteers, six of whom were women and four men with a mean age of 37.3 years (21 to 58). All the blood samples were allowed to clot for up to 30 minutes at room temperature

Fig. 1a

Fig. 1b

Figure 1a – Mean (SD) circulating serum levels of IL-6 obtained from patients in the various groups within hours of injury (*, significant difference compared with the phlebotomy control group, healthy volunteers and patients with fracture only). Figure 1b – Changes in circulating serum levels with time in patients who had sustained both a head injury and fracture.

and were spun at 1540 g for ten minutes. Serum was removed and stored at -80°C until use.

The serum was thawed at room temperature, mixed thoroughly before use and the levels of IL-6, sIL-6R and sgp130 were measured by enzyme-linked immunosorbent assay (ELISA; R&D Systems Europe Ltd, Abingdon, UK) following the manufacturers' instructions. The minimal detectable amounts of IL-6, sIL-6R and sgp130 were <0.2 pg/ml, 6.5 pg/ml and <0.05 ng/ml, respectively.

Statistical analysis. Shapiro-Wilk's test of normality was performed. Data, which were not normally distributed were transformed logarithmically and retested to ensure normal distribution before analysis by univariate ANOVA. Further analysis using the Levene test showed equality of variances between groups after logarithmic transformation. Student's *t*-test with Bonferroni correction was used to identify differences between groups with significance at the 0.05 level.

Results

Age and gender had no effect on the circulating levels of IL-6, sIL-6R or sgp130 and no significant difference in the levels of these factors between the phlebotomy control group and the healthy volunteers.

Levels of IL-6 within 12 hours of admission. The circulating level of IL-6 in serum was found to be significantly higher in patients who had sustained both head injury and fracture compared with the phlebotomy control group ($p = 0.005$) and the healthy volunteers ($p = 0.008$) (Fig. 1a). Several of the patients with either head injury only or fracture only showed high circulating levels of IL-6 but the means of these groups were not significantly greater than those of the control groups. When compared with patients who had sustained fractures only, those who had a head injury with fracture had a significantly raised level of circulating IL-6 ($p = 0.009$; Fig. 1a).

Changes in the level of IL-6 in serum with time. There was no significant change in the concentration of IL-6 between the initial samples and those taken one week after injury in patients who had sustained both a head injury and fracture ($p = 0.348$; Fig. 1b). These levels did not return to that found in healthy volunteers in the time period used in our study.

Levels of soluble IL-6 receptor within 12 hours of admission. There were no differences between groups of patients when the mean levels of circulating sIL-6R at the initial time points were considered ($p = 0.339$; Fig. 2a).

Changes in the level of sIL-6R in serum with time. The circulating level of sIL-6R in serum one week after injury was significantly higher in patients who had sustained a head injury with and without fracture compared with the initial sample ($p = 0.012$ and $p = 0.011$, respectively; Figs 2b and 2c), but this was not significant after two weeks.

Levels of sgp130 within 12 hours of admission. Levels of sgp130 were significantly lower in patients who had sustained a head injury with and without fracture compared with those who had sustained a fracture only ($p < 0.001$ and $p = 0.026$; Fig. 3a). Patients who had suffered both a head injury and fracture had significantly lower levels of sgp130 compared with the phlebotomy control group and healthy volunteers ($p < 0.001$; Fig. 3a).

Changes in the level of sgp130 in serum with time. There was a significant increase in the level of sgp130 in patients who had sustained both a head injury and fracture after one week compared with the initial time point ($p = 0.022$; Fig. 3b).

Discussion

Our study has shown that the circulating level of IL-6 is significantly raised in patients who have sustained head injury and fracture compared with uninjured control subjects and that the level remained high at later time points. The serum

Fig. 2a

Fig. 2b

Fig. 2c

Mean (SD) circulating serum levels obtained from patients a) within hours of injury b) over a period of time in those who had sustained both a head injury and fracture and c) over a period of time in those who had had a head injury.

Fig. 3a

Fig. 3b

Mean (SD) circulating levels of sgp130 in a) patients within hours of injury and b) with time in patients who had had both a head injury and fracture (*, significant differences compared with the phlebotomy control group and healthy volunteers; † significant difference compared with patients with fracture).

levels of sIL-6R were not significantly different between the groups of patients at the initial time point, but increased significantly after one week in those who had sustained both a head injury and fracture. Our study also showed lower levels of circulating sgp130 in patients who had sustained a head injury with and without fracture, which increased one week after the injury. We propose a mechanism based on the results of our study to explain the relationship between head injury and healing of a fracture whereby the altered levels of IL-6, sIL-6R and sgp130, observed in patients with head injury, stimulate cells within the fracture callus leading to altered repair of the fracture.

It has been reported that sIL-6R potentiates the agonistic effects of IL-6 in cell lines or gene-transfected cells.^{15,32-36} We suggest that while the serum levels of sIL-6R do not vary initially between our five groups of patients, it is the circulating level of IL-6 immediately after injury which may be important in modifying cell responses. Levels of IL-6 were greater in some patients with a fracture alone than in healthy individuals suggesting release after trauma. This is in agreement with previously published data.^{20-24,37,38} However, IL-6 is elevated to a much greater level in patients who have sustained a head injury and we postulate that this may be, in part, responsible for stimulating the early stages of the repair of a fracture within hours of trauma. In addition to this, the lower levels of sgp130 in these patients may reduce antagonistic binding to either IL-6 or IL-6/sIL-6R enhancing a possible role of IL-6 in the repair of a fracture seen in patients with severe head injury. The resulting increased level of the circulating IL-6/sIL-6R complex may be capable of stimulating cells of the mesenchymal lineage and therefore increasing the formation of osteoblastic bone.

A week following trauma, the levels of IL-6 in patients with both head injury and fracture had decreased but remained higher than in non-injured control subjects. This, in combination with increased sIL-6R, may be capable of sustaining an effect on the repair of a fracture by forming the IL-6/sIL-6R complex and maintaining agonist activity at the site of the fracture.

A number of studies have shown the circulating level of IL-6 to be raised in a variety of conditions such as alcoholic liver disease³⁹ and various rheumatological diseases.^{37,40} Hack et al⁴¹ found that increased plasma levels of IL-6 correlated with physiological markers of sepsis, and although no patients in our study showed signs of sepsis, this potential influence cannot be eliminated. Trauma itself may also be associated with increased IL-6 since Taniguchi et al,³⁸ have shown that levels of plasma IL-6 were elevated after chest and abdominal trauma. They do not report details of head injury or fractures, however, and it is therefore difficult to isolate the effects of trauma alone.

There are also conflicting reports suggesting that levels of IL-6 may correlate with the severity of injury or the clinical outcome.^{20,31,42-44} However, we found that the levels of IL-6, sIL-6R and sgp130 did not correlate with the GCS score.

In conclusion, we have shown changes in the profiles of IL-6, sIL-6R and sgp130 and propose a mechanism by which altered repair of a fracture may occur in patients with head injury. If this finding is confirmed by further *in vitro* and *in vivo* studies, this will indicate that the activity of circulating IL-6, either alone or in combination with its soluble receptor, could stimulate the early stages of repair of a fracture. This finding would lead to studies aimed at evaluating the usefulness of administering these cytokines to promote healing of a fracture.

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