Do traumatic brain injuries lead to accelerated fracture healing?

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Abstract
Introduction
Fracture healing can be defined as the physiological restoration of bone tissue, structure and function. A common association seen in orthopaedic practice is accelerated fracture healing, with exuberant callus formation in patients, with concomitant head injuries. This review explores our current state of understanding of this relationship.

Materials and methods
EMBASE and MEDLINE searches (Search terms: “traumatic brain injury” AND “fractures”; “head injury” AND “fractures”; “traumatic brain injury” AND “fracture healing”; “head injury” AND “fracture healing”) were performed in January 2014. Further, the author canvassed the reference lists of selected articles and online search engines such as Google Scholar.

Results
Few studies have examined the relationship between traumatic brain injury (TBI) and accelerated fracture healing, with conflicting results. Studies, to date, have either been retrospective studies or analyses of case series with relatively small number of patients. In some studies control groups have been used, whereas in others, reference has been made to fracture healing norms in the general population.

Discussion
Several hypotheses have been put forth to explain the link between TBI and accelerated fracture healing. Traumatic brain injury leads to a release of interleukin-6, BMP and prolactin. Local alkalinity at the fracture site, secondary to hyperventilation, and the release of basic fibroblast growth factors result in enhanced callus formation, which may represent true callus or be a variant of heterotropic ossification.

Conclusion
Studies on the effect of traumatic brain injury on accelerated fracture healing have yielded conflicting results. The author proposes a combined mechanism for this association. Further basic research and clinical work is needed to better define this relationship.

Fracture healing can be defined as the physiological restoration of bone tissue, structure and function. Orthopaedic dictum teaches that fractures of long bones, when associated with head injuries, frequently heal with excessive callus and at a faster rate than normal. The evidence for this, however, is flimsy, and dates back to a small series of patients treated in 1964 using multiple modalities and without an adequate control series. In 1968, Roberts first described heterotropic ossification (HO) of the elbow in patients with cerebral injury and a prolonged period of coma. The incidence of heterotropic ossification after traumatic brain injury (TBI) is up to 22%. In their study of 111 patients, Citta-Pietrolungo, Alexander and Steg found that the hip was most commonly affected site of HO, with patients having both asymptomatic and symptomatic sites of disease, as well as multiple sites of disease. The formation of HO can be a very rapid process, with mineralized bone developing from immature osteoid in a matter of weeks.

The alleged link between TBI and accelerated fracture healing remains a controversy. In patients who have sustained a TBI, with an associated extremity fracture, there is often a clinical perception that the rate and volume of new bone formation around the fracture site are increased. At our institute, we commonly see this association (Figure 1). Whether this rapidly forming new bone is fracture callus, or a variant of HO, remains a subject of debate. The aim of this study is to review the available literature to understand the relationship between TBI and accelerated fracture healing.

Materials and methods
The author performed EMBASE and MEDLINE searches (Search terms: “traumatic brain injury” AND “fractures”; “head injury” AND “fractures”; “traumatic brain injury” AND “fracture healing”; “head injury” AND “fracture healing”) in January 2014. Synonyms of these search terms were also used. Further, the author canvassed the reference lists of selected articles and online search engines such as Google Scholar.

Results
Few studies have examined the relationship between TBI and accelerated fracture healing (Table 1). Studies, to date, have either been retrospective studies or analyses of patients treated in 1964 using multiple modalities and without an adequate control series. In 1968, Roberts first described heterotropic ossification (HO) of the elbow in patients with cerebral injury and a prolonged period of coma. The incidence of heterotropic ossification after traumatic brain injury (TBI) is up to 22%. In their study of 111 patients, Citta-Pietrolungo, Alexander and Steg found that the hip was most commonly affected site of HO, with patients having both asymptomatic and symptomatic sites of disease, as well as multiple sites of disease. The formation of HO can be a very rapid process, with mineralized bone developing from immature osteoid in a matter of weeks.

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Figure 1: A case of humerus delayed union with traumatic brain injury. The patient presented to our institution 3 months after the injury exhibiting exuberant callus formation at the site of fracture.

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case series with relatively small number of patients. In some studies, control groups have been used (Table 1) whereas, in others reference has been made to fracture healing norms in the general population. Interestingly, Yang et al. in their study of treatment of femoral shaft fractures in head injury patients, and control with closed reduction and IM nailing, not only found a significantly increased time to the basic callus formation, but also an increased mean callus thickness in the head injury group. The severity or type of head injury was not significant. The finding of increased callus diameter was also reported in the study by Giannoudis et al.

Discussion

Theories

Several hypotheses have been put forth to explain the link between TBI and accelerated fracture healing. Although some hypothesis, such as elevation of somatotropin levels and trophic nerve fibres, have fallen out of repute, other theories continue to flourish.

One hypothesis is based on the observation that many patients with TBI are hyperventilated in an attempt to lower intracranial pressure by reducing pCO2. As a secondary outcome, their blood pH becomes alkalotic. Experimental studies have shown that alkaline pH promotes calcium precipitation. Newman et al., in their series of 13 patients with head injuries found that the mean pH was alkalotic (7.49) and suggested that this alkaline pH promotes alkalinity at the fracture site, which leads to calcium deposition which accelerates callus formation. A limitation of this study was the lack of a control group.

Local and systemic factors have also been implicated in accelerate fracture healing in TBI patients. In a rat osteoblast culture study, where serum from TBI patients was compared with control serum, a significant increase in cellular proliferation of osteoblasts was seen, suggesting that some circulating growth factor is elevated in TBI patients, which secondarily promotes osteoblastic activity.

Wildburger suggested that high serum prolactin levels observed during the 5th week post-injury in patients with TBI could account for the enhanced osteogenesis. This peak coincided with the appearance of HO and the period when fracture consolidation is typically understood to commence. Interestingly, other studied hormones such as cortisol, growth hormone and ACTH were not found to be significantly elevated. However, prolactin has been shown in a rat study to have minimal effects on osteogenesis compared to growth hormone suggesting that the elevated prolactin levels, in the works of Wildburger, are likely not directly responsible for enhanced osteogenesis and they may act by mediating a molecular cascade. Another study found that serum levels of ALP and precursor of type I collagen are elevated in patients with head injury compared to healthy controls, however no relationship to enhanced osteogenesis was found. Thus hormonal influences seem to have no direct effect on enhanced osteogenesis, but may work via an indirect mechanism.

Basic fibroblast growth factor is involved in the normal fracture healing process. Although the physiologic role of bFGF in bone metabolism still remains undefined, it has been shown to stimulate proliferation and differentiation of costal chondrocytes in vitro as well as chondrocyte proliferation and cartilage healing in vivo. Further, osteoblasts themselves synthesize bFGF, with a rat study showing that IV administration of bFGF results in dramatic hyperostosis. Levels of bFGF increase three-fold post-fractures, and increase seven-fold post TBI, which is seen even within the first week after injury. A second peak in bFGF was seen in the fourth post-traumatic week, which corresponded with clinical evidence of callus. A third peak was observed in the 7th-8th post-trauma week which the authors suggested could be a consequence of abundant callus formation at that time. Serum from fracture patients with TBI and without TBI were compared in fibroblast cell culture lines, however, the authors failed to show any causal relationship between bFGF and enhanced fibroblastic activity.

More recently, there has been an interest in the effect of inflammatory cytokines on the process of bone healing. Interleukin-6 (IL-6) is abundantly secreted by osteogenic cells and its deficiency results in increased inflammatory bone

![Figure 2: Proposed combined mechanism flowchart for association between traumatic brain injury and enhanced callus formation.](image-url)
et al, they found that the rate of fracture union was not increased in TBI patients and in fact there was evidence of delayed fracture healing\(^6,9,10\). The authors suggested that new bone seen at fracture sites in TBI patients represents a form of HO, consistent with their finding of up to 52% rate of HO across the three studies. A limitation of this group of studies is that no control group was used, with comparisons made to general fracture healing norms.

**Proposed combined theory**

The author's proposed mechanism of the interaction between TBI and enhanced fracture healing is represented in figure 2. The patient, who has suffered an extremity injury, is either hyperventilated or not in the acute period, with resulting alkalosis and release of basic fibroblast growth factor. There may also be an intermediate effect of elevated BMP and IL-6 levels. This promotes calcium deposition and cell activity at the fracture site with resulting enhanced callus formation seen clinically or radiologically. This callus may represent HO or true callus. The author has not given a timeline as it is still to be proved conclusively whether the rate of healing is enhanced by TBI.

**Conclusion**

Studies on the effect of traumatic brain injury on accelerated fracture healing have yielded conflicting results, with some showing accelerated healing while others showing no effect and even delayed union. The author proposes a combined mechanism for this association based on the available literature. Further basic research and clinical work is needed to better define this relationship.

**References**


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**Table 1: Studies exploring the association between traumatic brain injury and accelerated fracture healing (adapted from 4).**

<table>
<thead>
<tr>
<th>Study</th>
<th>Accelerated bone healing</th>
<th>Bone studied</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Mean time to union in head injury group (days)</th>
<th>Mean time to union control group (days)</th>
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<td>Newman et al. (5)</td>
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<td>Non-operative</td>
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<td>IM nail vs non-operative</td>
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<td>Spencer et al. (7)</td>
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*IM = intramedullary; CRIF = closed reduction and internal fixation; ORIF = open reduction and internal fixation*

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