

## CLINICAL STUDY OF FRACTURE HEALING IN PATIENTS WITH BRAIN NERVE INJURY

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### ABSTRACT

**Objective:** To study the effects of limb fracture combined with cranial nerve injury on bone mineral density, bone microstructure and bone metabolism.

**Method:** 42 patients were randomly divided into simple fracture group and brain injury and fracture group. Serum samples, bone mineral density and levels of serum amino-terminal peptides and osteocalcin were analyzed at 3rd week, 6th week and 3rd month after operation.

**Results:** compared with the fracture group, the volume fraction of the cancellous bone, the thickness of the trabecular bone, the total area of the tibial cortical cross section, serum collagen N telopeptide and osteocalcin level of the brain injury and fracture group were significantly higher in the 3rd and 6th week after operation, and there was no significant difference between the two groups 3 months after the operation.

**Conclusion:** cranial nerve injury can increase local bone mineral density and improve bone microstructure so that to promote bone healing and bone metabolism.

**Keywords:** Fracture, Cranial Nerve Injury, Fracture Healing.

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### Introduction

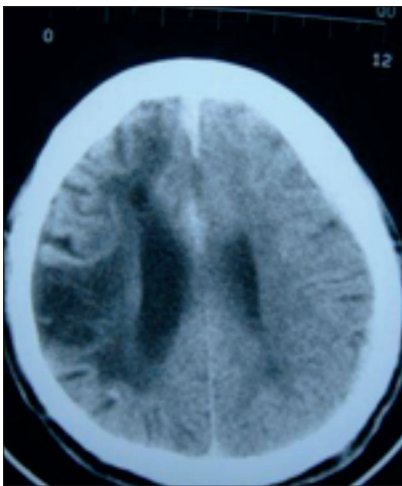
As early as in 1964, some scholars first published the article, pointing out that the fracture healing of the patients with brain injury was obviously accelerated, and the amount of callus formation was significantly increased<sup>(1)</sup>. In 70s, some scholars found and confirmed the same phenomenon, which they called "heterotopic ossification"<sup>(2-3)</sup>. In 1987, a study put forward the application of strict statistical treatment to compare the healing condition of the patient with bone fracture as well as brain injury and those only with a fracture, and the same conclusion was drawn<sup>(4-5)</sup>.

Some scholars have reported the healing of tibial fracture patients with brain injury, the heal-

ing of patients with femoral fractures and different brain injuries, and that of spinal cord injury patients. Through a large number of clinical observations and statistical studies, it is proved that the rate of ectopic ossification in the patients with brain injury and spinal cord injury is significantly higher. Heterotopic ossification is more common in Cervical spinal cord and upper thoracic spinal cord injuries<sup>(6)</sup>.

Some researches show that there was no case of heterotopic ossification in patients with injuries in the lumbar segment. Some studies also confirmed that the occurrence of ectopic ossification is closely related to loss of motor function, but patients only suffer from the loss of sensory function do not suffer from heterotopic ossification.

However, agreement has not reached on the incidence of heterotopic ossification in incomplete paralyzed and completely paralyzed persons<sup>(7)</sup>. It is reported that there are 85 cases of heterotopic ossification in 654 cases of spinal cord injury. The incidence of heterotopic ossification in spasmodic patients is significantly higher than those without spasms. The incidence of heterotopic ossification in simple spinal cord injury was not consistent, ranging from 1% to 50% while most of the reported incidence rates were between 20%-30%, and the incidence of children was lower than that of adults, which may be related to thymic function<sup>(8-10)</sup>. Ectopic ossification may occur at least 18 days after spinal cord injury, but it also may occur 1 year after injury. The common occurrence time is 1-4 months. The incidence rate of male was 2 times as high as that of female<sup>(11)</sup>. 209 patients with acute spinal cord injury were investigated. The incidence rate of ectopic ossification and deep vein thrombosis were 14.3% and 16.7% respectively, and the rate of suffering the two in one person was 5.3%, which has significant statistical correlation<sup>(12)</sup>. Compared with patients only with fractures, the healing time of those with heterotopic ossification and deep vein thrombosis occurring in the same side of the lower limbs combined with central nervous system (brain and spinal cord) injury (see Figure 1) shortened by about 1/3, the mechanism of which are still in vague, which cannot be explained till now<sup>(13)</sup>.



**Fig 1:** Central nervous system injury.

Alkalosis: experiments on animals show that the local pH value increases when callus forms. Therefore, some people think that respiratory alkalosis caused by the hyperventilation of the patients with brain injury may contribute to the formation and mineralization of the callus.

Hormone regulation: some scholars believed that after brain injury, the endocrine system secretes more growth hormone, thyroid stimulating hormone, triiodothyronine (T3), thyroxine (T4), and insulin, which can promote fracture healing.

Heterotopic ossification: patients with brain injury often have ectopic ossification around the joints. Research compared 53 cases of severe brain injury combined with limb fracture and 30 cases of simple limb fracture. According to quantitative determination of the diameter of the callus and the healing time observed by X-ray, calluses in the part of bone fracture of the patient with brain injury are obvious.

In a word, many cells are involved in the process of fracture healing, and the effects of these growth factors are different. Synergisminteraction can be found between each of them, under the effect of which the fracture heals.

## Methods

### *Research object and method*

Group and intervention: 42 patients were divided into the group of simple fracture and the group of brain injury combined with fracture, each of which has 21 subjects.

Measurement of tibia bone mineral density: bone mineral density (BMD) of the tibia was measured by dual energy X ray absorptiometry. The scanning speed is 1mm/s and the resolution speed is 0.5mm \*0.5mm. High resolution density analysis software was used to scan the proximal tibia and analyze the BMD (mg/cm<sup>2</sup>). The measurement was repeated 3 times. The coefficient of variation between groups was less than 2.0%. Micro-CT test: Micro-CT with a resolution of 10μm was used to scan the middle and distal femur. The scanning length of the distal femur was 3mm (and 300 layers were scanned).

The cortical bone and cancellous bone microstructure of proximal tibial metaphysis were analyzed by Micro-CT with a resolution of 10μm. Micro-CT was used to scan the metaphyseal bone and cortical bone of the tibial diaphysis to obtain a continuous Micro-CT fault image with a resolution of 1024 x 1024. The thickness of the scanning layer was 36μm×36μm×36μm; the gray level is 16bit; and the interlayer spacing is 6μm. Semi-automatic method is used to select the region of interest. After the Gauss filter, a visible fixed threshold is used to distinguish the structure of the bone and

medullary cavity. The cancellous bone region of 1.0-5.0mm distal growth plate is used to analyze the microstructure of the trabecular bone. This is to avoid the interference of the primary ossification center to the measurement. The middle segment of the backbone is used to analyze the geometric structure of the cortical bone.

Microstructural parameters of the metaphyseal cancellous bone of the tibial metaphysis measured by the built-in software of Micro-CT include the analysis of bone volume and trabecular distribution, calculation of the volume fraction and the thickness of bone trabecula. The geometric parameters of the cortical bone in the middle part of the tibia include the total area of the cross section and the area of the medullary cavity.

The measurement of the level of serum amino-terminal peptides and osteocalcin: aseptic tube is used to collect the venous blood of the patient, which is then centrifugated and preserved at -80°C; enzyme-linked immunosorbent assay (ELISA, Shanghai MATHA company's kit) was used to measure the level of serum amino-terminal peptides and osteocalcin. ELISA method uses Bio-Tek microplate reader in the test. The unit of I type collagen N telopeptide

**Main observation indexes**

Bone mineral density, bone volume fraction, trabecular thickness, total area of cross section, levels of serum amino-terminal peptides and osteocalcin were measured in each group.

**Statistical analysis**

The measurement data were expressed in  $\bar{x} \pm s$ , and the data were processed by SPSS16.0 software. The single factor analysis of variance was used for the comparison between groups. There was significant difference with  $P < 0.05$ .

**Results and discussion**

**Bone mineral density changes in the proximal tibia**

Compared with the group only with fractures, the bone mineral density of the proximal tibia was significantly increased in 3 weeks and 6 weeks after injury ( $P < 0.05$ ). The bone mineral density of the proximal tibia of the 2 groups had no significant difference after 3 months (Table 1).

Groups	Bone density score		
	After 3 weeks	After 6 weeks	After 3 months
Simple fracture group	14.38±0.025	0.157±0.027	0.227±0.012
Fracture combined with cranial nerve injury group	0.152±0.027	0.247±0.023 <sup>a</sup>	0.224±0.027

**Table 1:** Bone density score.

Note: Compared with the simple fracture group, <sup>a</sup> $P < 0.05$ .

**Comparison of the microstructural parameters of tibial cancellous bone**

Micro-CT results show that compared with the fracture group, after 3 and 6 weeks, the microstructural bone volume of the proximal tibial cancellous bone and the thickness of trabecular bone were significantly increased ( $P < 0.05$ ) (Table 2, 3) in the group of fractures and brain injuries. The geometric structure of the proximal tibial bone: the total area of the cortical bone section and the area of bone marrow cavity of the tibial cortex were significantly higher than those of the fracture group ( $P < 0.05$ ) at the last 3 weeks and 6 weeks, and there was no significant difference in the area of bone marrow cavity of the two groups (Table 4).

Groups	Bone volume fraction		
	After 3 weeks	After 6 weeks	After 3 months
Simple fracture group	14.38±3.42	25.67±2.54	33.17±2.43
Fracture combined with cranial nerve injury group	24.45±4.16	33.60±3.32a	35.17±2.43

**Table 2:** Bone volume fraction.

Note: Compared with the simple fracture group, <sup>a</sup> $P < 0.05$ .

Groups	Trabecular density		
	After 3 weeks	After 6 weeks	After 3 months
Simple fracture group	24.36±5.12	38.74±5.08	53.39±5.16
Fracture combined with cranial nerve injury group	38.74±5.57	54.97±6.77a	55.63±4.89

**Table 3:** Trabecular density.

Note: Compared with the simple fracture group, <sup>a</sup> $P < 0.05$ .

Groups	Total area of section		
	After 3 weeks	After 6 weeks	After 3 months
Simple fracture group	9.18±0.41	8.63±0.58	6.96±0.57
Fracture combined with cranial nerve injury group	11.75±0.86	9.72±0.82a	6.72±0.82

**Table 4:** Total area of section.

Note: Compared with the simple fracture group, <sup>a</sup> $P < 0.05$ .

### **Changes of serum amino-terminal peptides and osteocalcin levels**

After 3 and 6 weeks, the level of serum amino-terminal peptides and osteocalcin in the group of brain injuries combined with fractures was significantly higher than that of the simple fracture group ( $P < 0.05$ ), and there was no significant difference in the level of serum amino-terminal peptides and osteocalcin in the two groups after 3 months (table 5, 6).

Groups	Comparison of serum amino-terminal peptides		
	After 3 weeks	After 6 weeks	After 3 months
Simple fracture group	20.41±5.45	19.41±4.75	16.71±6.21
Fracture combined with cranial nerve injury group	29.83±6.36	24.43±6.76 <sup>a</sup>	17.90±6.61

**Table 5:** Comparison of serum amino-terminal peptides.  
Note: Compared with the simple fracture group, <sup>a</sup> $P < 0.05$ .

Groups	Comparison of osteocalcin levels		
	After 3 weeks	After 6 weeks	After 3 months
Simple fracture group	14.99±5.47	12.18±4.86	10.69±4.73
Fracture combined with cranial nerve injury group	18.39±4.26	15.73±5.17 <sup>a</sup>	11.23±5.13

**Table 6:** Comparison of osteocalcin levels.  
Note: Compared with the simple fracture group, <sup>a</sup> $P < 0.05$ .

### **Conclusion and outlook**

#### ***Brain injuries affects fracture healing***

It is found that the patients with fractures and brain injuries have the characteristics of early osteogenic callus, more callus growth and shorter healing time compared with patients with only fractures. The present results show that the acceleration of fracture healing after brain injury may be mainly due to the adjustment of body fluid factors, especially growth factors, which play an important role in promoting fracture healing in the case of fractures and brain injuries.

#### ***Brain injuries increase the bone mineral density around the fracture***

Bone mineral density is usually used to measure to the bone mass. It is the most commonly used standard for diagnosing osteoporosis, and is also considered as the main predictor of fracture healing. Neural growth factors can promote the synthesis of neurotrophic substances in motor neurons and promote the recovery of calcium pump activity in skeletal muscles.

A large number of clinical and experimental studies have found that the acceleration of fracture healing after fracture and brain injury may be related to the early-coming and long-lasting peak of the expression of growth factors in the body.

#### ***Brain injuries improve the bone microstructure around the fracture***

In addition to bone mass, bone microstructure is also an important factor affecting bone strength. It is the decisive factor of bone brittleness and is independent from bone density. A noninvasive method for bone structure analysis is used to predict fracture risk and finds that the bone trabecular is more sensitive than bone mineral density to changes. The results of the experimental study showed that compared with the simple fracture group, the microstructural bone volume fraction of the proximal tibial cancellous bone and the thickness of the bone trabecular in the proximal tibia were significantly increased in the group of fractures and brain injuries after 3 and 6 weeks, and the total area of the tibial cortical cross section was significantly larger than that of the simple fracture group at 3rd week. The results of bone mechanics test also coincide with bone microstructure data.

#### ***Brain injuries promote the activity of the osteocytes and osteoclasts and improve the bone turnover in the healing process***

Osteocytes and Osteoclasts play an important role in bone healing. Osteocalcin is the most important index to evaluate osteoblast activity, which directly reflects the activity of osteoblasts and changes in bone physiological metabolism. The results showed that the level of serum amino-terminal peptides and osteocalcin in the group of brain injury combined with fracture was higher than that of the simple fracture group as well as the sham-operated group at 3rd week and 3rd month, indicating that the osteocytes and osteoclasts were active in the healing process after the brain injury, and the bone turnover and fracture healing were thus improved.

To sum up, the levels of bone mineral density, and the serum amino-terminal peptides and osteocalcin of the patients with brain injuries were significantly higher than those in the simple fracture group. Although the mechanism of brain injury to promote fracture healing is not fully elucidated, the result suggests that this process may be associated with the high bone turnover promoted by brain injuries.

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