Int. J. Morphol.,
43(2):759-765, 2025.

Influence of Bone Marrow Enriched Bone Grafting Versus Traditional Bone Grafting in Callus Formation and Bone Growth Factors of Patients with Tibial Fracture and Bone Defect

Influencia del Injerto Óseo Enriquecido con Médula Ósea frente al Injerto Óseo Tradicional en la Formación de Callos y los Factores de Crecimiento Óseo de Pacientes con Fractura de Tibia y Defecto Óseo

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XU, Q.; WENG, H.; ZHU, L.; WU, M. & MEI, Z. Influence of bone marrow enriched bone grafting versus traditional bone grafting in callus formation and bone growth factors of patients with tibial fracture and bone defect. *Int. J. Morphol., 43(3)*:759-765, 2025.

SUMMARY: Bone defects are a common orthopedic trauma in clinical practice. Limb amputation has been used in the past, but its disadvantages are evident. Autogenous bones are widely recognized in modern medicine as the gold standard for bone graft fusion due to its strong osteoinductive properties, good osteogenicity, and low cost. Seventy patients diagnosed with distal infectious bone defect (DIBD) after tibial fracture (TF) were randomly assigned to an observation (Obs) group (n = 35) and a control (Ctrl) group (n = 35). Bone marrow enriched bone graft surgery (BME-BGS) and traditional bone graft surgery (T-BGS) were performed in the Obs and Ctrl groups, respectively, for comparison. The time for disappearance of the fracture line (T-DFL) and the time for fracture healing (T-FH) were considerably shorter in the Obs group (P<0.05). The postoperative callus formation score (CFS), bone morphogenetic protein (BMP), transforming growth factor (TGF)-β, and alkaline fibroblast growth factor (AFGF) levels in the Obs group were sharply higher (P<0.05). Furthermore, treatment effectiveness rate (TER) in Obs group was considerably higher (P<0.05). Meanwhile, incidence of complications (IOC) in Obs group (11.43 %) was higher to 20 % in Ctrl group (P<0.05). Compared with T-BGS, the BME-BGS can effectively shorten the T-DFL in patients with DIBD after TF, promote the secretion of osteogenic induction factors and callus formation, and effectively improve the efficacy of fracture end healing, with clinical safety.

KEY WORDS: Bone defect; Tibial fracture; Callus formation; Bone marrow enriched bone graft surgery; Bone growth factor.

INTRODUCTION

Tibial plateau fractures often occur after traffic accidents or severe impact injuries. However, sports-related injuries, falls, and other minor traumatic events can also cause these fractures, especially in elderly individuals with osteoporosis (Li *et al*., 2023). In young and middle-aged individuals, tibial plateau fractures are commonly split fractures, while in the elderly, they often present as compression fractures. Following a tibial plateau fracture, the affected knee joint may exhibit swelling, pain, difficulty bearing weight, and impaired walking. Tension blisters on the skin may also develop. Fractures can be accompanied by meniscus damage, knee joint dislocation, rupture of the cruciate and collateral ligaments, vascular and peroneal nerve injuries, and, in severe cases, compartment syndrome. Open tibial plateau fractures often involve significant soft tissue damage and may even result in bone defects. Treating these fractures requires high clinical decision-making skills, considerable time, and meticulous attention due to the complex nature of the injuries (Zhang *et al*., 2020).

Before the advent of microsurgery and free tissue transplantation, limb amputation was almost the sole option for treating bone defects. In recent years, various aspects of medicine, including tissue engineering, have made significant advancements. However, bone defects remain a challenging condition, with a persistently high amputation rate (Aktuglu *et al*., 2019; Andrzejowski *et al*., 2020; Suda 2020). Treatment and repair methods for bone defects primarily include bone grafting, the Ilizarov technique, membrane-induced regeneration, gene therapy, and bone

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Qiang Xu and Hao Weng contribute equally to this work as co-first author.
FUNDING. This research is supported by Science and Technology Planning Project of Qijiang District, Chongqing, China (No. 2023035).

Received: 2025-01-01 Accepted: 2025-03-02

tissue engineering technology. Bone marrow enriched bone grafting surgery (BME-BGS) generally falls into two major categories: autogenous bone grafting and allogeneic bone grafting, both of which are methods of bone grafting (Toepfer *et al*., 2015). Among these, autogenous bone grafting is the most commonly used clinical approach due to its excellent osteoinductive and osteogenic properties, which are widely considered the gold standard for bone graft fusion in modern medicine. Furthermore, the combination of flap transfer techniques and the Ilizarov technique utilizing flap transfer to repair soft tissue defects and the Ilizarov technique to restore bone tissue defects represents a developmental direction for the comprehensive repair of extensive limb tissue defects. This approach significantly shortens treatment time, enhances bone formation capacity, and increases infection resistance (Kotsougiani *et al*., 2018; Khmyzov *et al*., 2022). The advantages of membrane-guided tissue regeneration technique lie in its simple operative procedure and patient acceptability, making it suitable for widespread clinical application. It facilitates quicker healing of bone injuries, allowing for rapid restoration of bone tissue function within a short period. However, this technique requires a second surgery, posing a risk of secondary trauma to the patient and increasing surgical risks. Additionally, the limited availability of autogenous cancellous bone hinders its complete fulfillment of the bone volume required for transplantation in large bone defects (Lee *et al*., 2010; Cho *et al*., 2014; Tyler *et al*., 2015). Gene therapy involves introducing osteogenic genes into target cells or carriers, which then regulate the expression of bone-regenerative genes related to osteogenesis, thereby repairing bone defects. The advantages of gene therapy include the avoidance of stem cell screening and extraction, in vivo editing, sustained effects, and more effective repair of large bone defects. It also allows control over bone tissue growth and development during the repair process, preventing excessive growth and yielding better repair outcomes. However, its clinical safety requires further validation (Visser *et al*., 2019).

Altogether, autogenous BME-BGS finds widespread application in the repair and treatment of bone defects. However, its superiority compared to traditional bone grafting methods remains unclear. The aim was to comprehensively assess the clinical efficacy and safety of BME-BGS versus traditional bone graft surgery (T-BGS) in treating tibial fracture (TF) bone defect patients.

MATERIAL AND METHOD

Research subjects. This work selected 70 patients diagnosed with distal infectious bone defects (DIBD) after TF between January 2021 and January 2023 at the hospital as the research subjects. They were randomly grouped into two: 35 patients in the Observation group (Obs group) who underwent BME-BGS, and 35 patients in the Control group (Ctrl group) who underwent T-BGS. The patients included 41 male patients and 29 female patients, with ages ranging from 36 to 60 years. The study participants agreed to sign informed consent forms, with the understanding that their family members also consented to their participation. The implementation of this study has received approval from the hospital's ethics committee.

All patients were randomly grouped into two, as mentioned above, with 35 patients in each group. The baseline characteristics of the two groups were shown in Figure 1. In the Obs group, the mean age of the patients was 45.07 ± 3.95 years old, including 19 males and 16 females. The average duration of illness (DOI) was 7.86 ± 1.25 months, with a bone defect length (BDL) of 6.31 ± 0.74 cm. There were 14 cases of TF in the distal segment and 21 cases in the middle segment. In the Ctrl group, the mean age of patients was 47.12 ± 4.66 years old, including 22 males and 13 females. The average DOI was 7.43 ± 1.06 months, with a BDL of 6.09 ± 0.88 cm. There were 15 and 20 cases of TF in the distal and middle segment, respectively. No obvious difference was observed in age, sex, DOI, BDL, and the proportion of TF in the middle and distal segments for patients between the Obs and Ctrl groups (P>0.05).

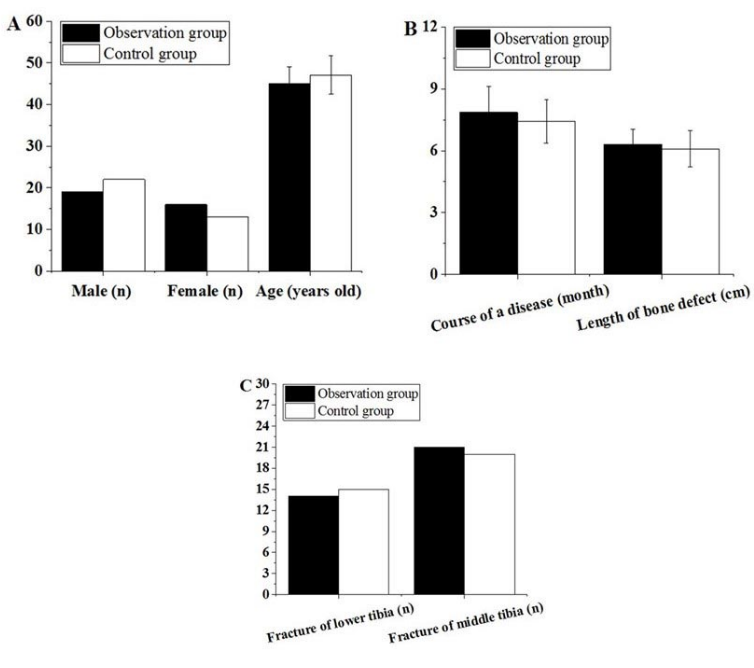

Fig. 1. Baseline characteristics of patients enrolled. (A: sex and age; B: DOI and BDL; C: proportion of TF in the middle and distal segments).

Patients enrolled in this work had to satisfy all the following conditions: I. patients with open fractures; II. those with complete medical records; III. those with clear consciousness and ability to communicate; IV. adult females; and V. patients who signed informed consent.

Patients who had any of the following conditions had to be excluded: I. patients unwilling to fully cooperate with the trial; II. patients with concurrent mental disorders; III. those with concomitant old fractures; IV. those with coagulation disorders; and V. patients with known drug allergies.

Preoperative treatments. Before surgery, it was essential to address any concurrent symptoms or conditions the patient may have, such as hypertension, anemia, diabetes, and hypoalbuminemia. Additionally, assessing and evaluating the stability of local soft tissues and fracture ends was crucial. Concurrently, collecting patient secretions for bacterial culture and sensitivity testing should be conducted to select appropriate antibiotics. In addition, X-ray imaging was utilized to determine the length of the bone defect, the presence of necrotic bone, and to calculate the required grafting volume.

Surgery schemess. The BME-BGS was employed in the Obs group. 1. Firstly, thorough debridement was performed, removing necrotic inflammatory tissue and dead bone until fresh bleeding was observed at the bone ends. The wound and the medullary cavity at the fracture site were repeatedly flushed with hydrogen peroxide, saline, and diluted iodine. Diluted iodine solution was poured into the wound to soak the medullary cavity and surrounding soft tissues. 2. Local infiltrative anesthesia was administered at the patient's bone marrow puncture site. Under X-ray guidance, a puncture was made to the fracture end, and the puncture needle was secured. Approximately 8 mL of bone marrow was aspirated from the patient. Subsequently, the bone marrow was slowly injected into the bone defect area. After a 5-minute waiting period, the needle was removed. 3. Sterile dressing with vaseline gauze was applied and the puncture site was firmly bandaged under pressure. Weekly injections were administered for four consecutive weeks.

The Ctrl group underwent skeletal bone grafting surgery. The patients were subjected to combined epidural anesthesia. A bone block was extracted from the anterior one-third of the iliac bone, and it was then placed at the fracture end before suturing the incision.

All patients underwent regular postoperative X-ray examinations until their bone defects had healed.

Postoperative treatments. After surgery, the patients were administered antibiotics for infection prevention. It was important to ensure the dryness of the incision dressing, with dressing changes performed daily as scheduled. In the early stages, necrotic bone with blackened epidermis was retained, and 7 weeks after surgery, the removal of this necrotic tissue was carried out. Once new granulation tissue covered the surface, skin grafting was performed.

Observation indicators and their determination. Fracture healing evaluation was conducted based on X-ray images, documenting time for fracture healing (T-FH) and time for disappearance of fracture line (T-DFL). The criteria for fracture healing were as follows: absence of tenderness at the fracture ends, normal mobility at the fracture site, blurry fracture line with continuous callus formation observed on X-ray images, absence of deformity at the fracture site during two weeks of continuous observation, the ability to lift a weight of 1 kg for 1 min with the upper limb raised when the external fixation was removed, and the ability to walk continuously for 3 min with the lower limb and take no fewer than 30 steps.

Three months after surgery, 6 mL of fasting venous blood samples were collected from the patients. Serum samples were obtained after centrifugation. Enzyme-linked immunosorbent assay (ELISA) was employed to measure the levels of bone morphogenetic protein (BMP), transforming growth factor-b (TGF-β), and acidic fibroblast growth factor (AFGF).

Callus formation assessment of patients was performed 3 months post-surgery, using the scoring criteria presented in Table I.

Table I. The criteria for callus formation score (CFS) of th patients.

Grade	X-ray findings	CFS
1	No callus formation observed at the fracture site.	0
2	Cloud-like callus formation observed at the fracture site.	1
3	Unilateral callus formation observed at the fracture site on anteroposterior view.	2
4	Bilateral callus formation observed at the fracture site on anteroposterior view.	3
5	Structurally formed callus.	4
6	Moderate absorption of external callus was observed.	5
7	There was a complete absorption of external callus.	6

Clinical efficacy was evaluated according to the Tohner-Wrnch criteria, categorized into three levels: excellent, good, and poor. The total effectiveness rate (TER, excellent and good combined) was calculated.

Postoperative follow-up included recording any complications experienced by the patients, such as angular deformity, wound infection, knee pain, and skin necrosis at the incision site. The incidence of complications (IOC) was calculated.

Methods for statistics. Data were analyzed using SPSS version 20.0. Descriptive statistics for continuous variables were presented as mean ± standard deviation, while categorical data were expressed as percentages (%). Between-group comparisons were performed using repeated measures analysis of variance (ANOVA), and within-group comparisons were conducted using two-way ANOVA. A two-tailed test with P<0.05 was considered statistically significant.

RESULTS

T-DFL and T-FH of patients in different groups. Figure 2 displayed the comparison results of T-DFL and T-FH of the patients between the Obs group and the Ctrl group. T-DFL for Obs group patients was 19.35 ± 3.31 weeks, and T-FH was 26.74 ± 4.01 weeks. For Ctrl group patients, the T-DFL was 26.44 ± 3.68 weeks, and T-FH was 30.81 ± 3.43 weeks. These results revealed that T-DFL and T-FH for Obs group patients were both much shorter in contrast to those for Ctrl group patients, exhibiting obvious differences (P< 0.05).

Comparison on postoperative levels of BGFs for patients. Figure 3 presented the postoperative levels of BGFs for patients in various groups. After surgery, the serum BMP, TGF-b, and AFGF levels for Obs group patients were 138.06 ± 11.24 pg/mL, 2497.41 ± 202.83 pg/mL, and 69.62 ± 5.05 pg/mL, respectively. For Ctrl group patients, the above indicators showed the levels of 109.44 ± 13.72 pg/mL, 1885.07 ± 175.01 pg/mL, and 50.71 ± 4.52 pg/mL, respectively. Thus, the postoperative levels of BMP, TGF-b, and AFGF in serum of patients in Obs group were sharply higher, exhibiting remarkable differences based on those in Ctrl group (P<0.05).

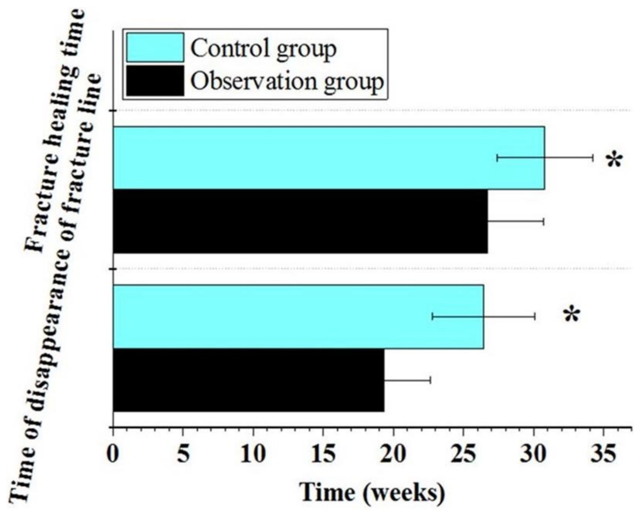

Fig. 2. Comparison of T-DFL and T-FH. Note: * suggested a great difference with *P*<0.05 to the Ctrl group.

Comparison on postoperative CFS of patients. Figure 4 illustrated the CFS at 3 months postoperatively for both patient groups. The postoperative CFS was 4.06 ± 0.51 in the Obs group and 2.17 ± 0.37 in the Ctrl group. As a results, the postoperative CFS for Obs group patients was higher in comparing to the score in Ctrl group, presenting a considerable difference with *P*<0.05.

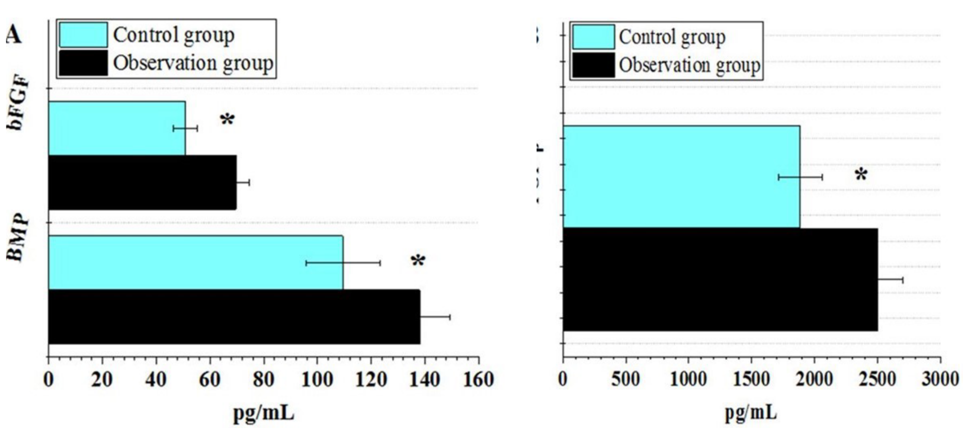

Fig .3. Comparison on postoperative levels of BGFs for patients. Note: * suggested a great difference with *P*<0.05 to the Ctrl group.

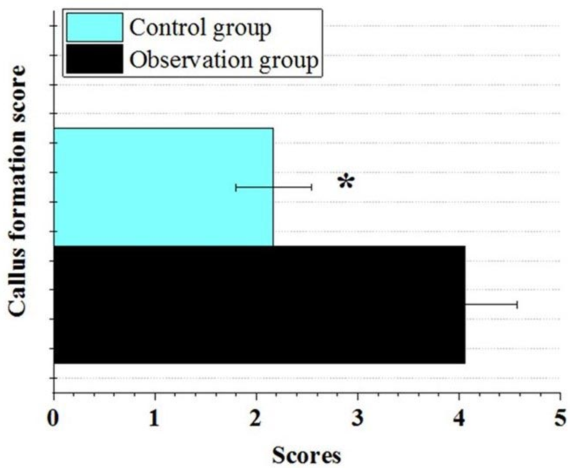

Fig. 4. Comparison on postoperative CFS of patients. Note: * suggested a great difference with $P<0.05$ to the Ctrl group.

Clinical efficacy in various groups. Figure 5 depicted the clinical efficacy in different groups for comparison. In the Obs group, 18 cases were rated as excellent, 15 cases as good, and 2 cases as poor, resulting in a TER of 94.29 %. In the Ctrl group, 11 cases were rated as excellent, 16 cases as good, and 8 cases as poor, yielding a TER of 77.14 %. The TER for patients in the Obs group was higher, which was greatly different from that in the Ctrl group ($P<0.05$).

Comparison on IOC of patients. Figure 6 illustrated the postoperative occurrences of angular deformity, wound infection, knee pain, skin necrosis at the incision site, and the IOC for both patient groups. In the Obs group, postoperatively, there was 1 case of angular deformity, 2 cases of wound infection, 1 case of knee pain, and no cases of skin necrosis at the incision site. In contrast, there were 2 cases of angular deformity, 2 cases of wound infection, 2 cases of knee pain, and 1 case of skin necrosis at the incision site in the Ctrl group. Therefore, the postoperative IOC for patients in the Obs group was much lower to that in the Ctrl group (11.43 % vs 20 %), showing obvious difference ($P<0.05$).

DISCUSSION

Bone defects are common orthopedic trauma condition, typically caused by trauma, infection, tumors, surgical debridement for osteomyelitis, and various congenital diseases. Treating substantial bone defects remains a clinical challenge. While amputation treatment in the past could expedite recovery, it inflicted significant physical and psychological impacts on patients (Cosman *et al*., 2019). Presently, the focus has shifted towards limb salvage treatment, which includes techniques such as bone shortening, bone transport, vascularized or non-vascularized

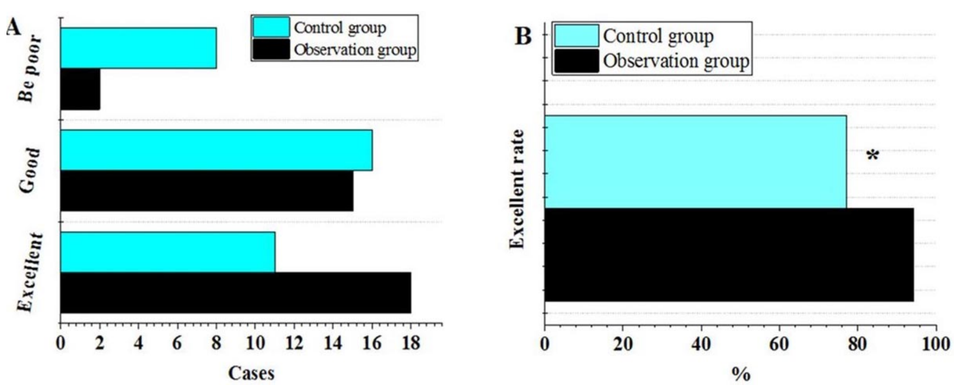

Fig. 5. Clinical efficacy in different groups. (A: number of patients with excellent, good, and poor efficacy; B: TER). Note: * suggested a great difference with P<0.05 to the Ctrl group.

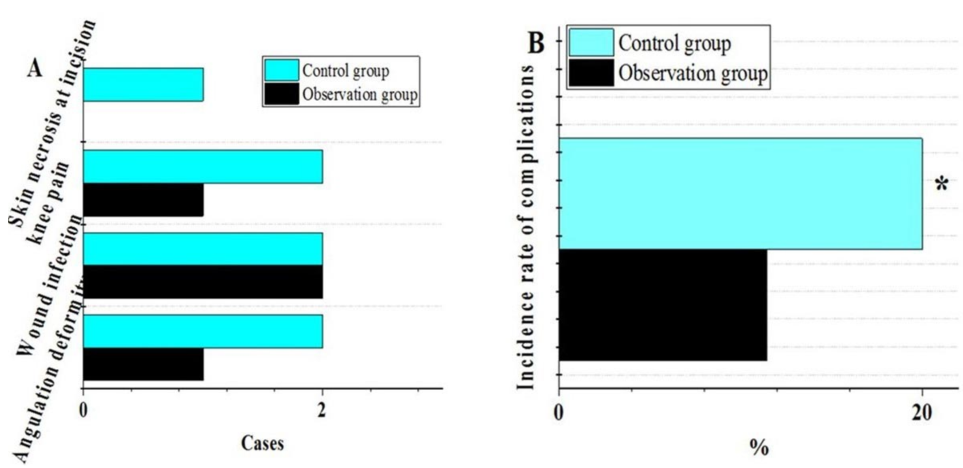

Fig. 6. Comparison on IOC of patients. Note: * suggested a great difference with $P<0.05$ to the Ctrl group.

bone grafting, and the use of bone substitutes. Among these, autogenous bone is generally considered the gold standard for bone fusion due to its strong osteoinductive properties, good osteogenicity, and cost-effectiveness. It is typically suitable for patients with bone defects of up to 6 cm in length and good local skin conditions (Durmus¸lar *et al*., 2016; Kotsougiani *et al*., 2017). In clinical therapeutic research, describing the baseline characteristics of the groups helps assess their comparability. The closer the baseline characteristics of patients in each group, the better the comparability between the groups. Thus, this work initially compared the baseline data of the two patient groups and found no significant differences in age, sex, DOI, BDL, and proportion of TF between the Obs group and Ctrl group. This provides reliability for subsequent intergroup data comparisons.

The fading of the fracture line usually takes about 2 months, although there may be variations based on different locations and degrees of the fracture. A blurry fracture line indicates significant callus growth at the local site and partial reconnection of the fracture ends (Kim *et al*., 2022). If there is no bone defect, malnutrition, or anemia at the fracture site, appropriate weight-bearing stimulation can gradually reshape the local callus along the direction of skeletal stress. Ultimately, the fracture ends become fully connected and the fracture line disappears. Additionally, the time for fracture healing refers to the duration required for diagnosis and treatment to reach a medically recognized state of recovery after bodily injury, with a typical recovery period of 6 months for T-FH (Main *et al*., 2014; Matsumoto & Goto, 2017). This work found that the T-DFL and T-FH of patients in the Obs group were sharply shorter than those in the Ctrl group, with a visible difference. This suggests that compared to T-BGS, BME-BGS effectively promote fracture healing and shortens the time for the fracture line to disappear. Growth factors are peptide substances that transmit information between cells and regulate cell growth. They are essential components of the core and key elements of tissue engineering along with seed cells and scaffold materials (Fu *et al*., 2011; Lu *et al*., 2016). Growth factors exert a vital role in cell proliferation, tissue or organ repair and regeneration (Cibulka *et al*., 1994). The postoperative levels of BMP, TGF-β, and AFGF were higher in the Obs group and exhibited obvious differences with those in the Ctrl group. This indicates that BME-BGS can effectively promote the secretion of osteogenic induction factors and nutrients among patients, leading to improved healing of the fracture ends.

The postoperative CFS of patients in the Obs group was higher in comparison to the Ctrl group, with a substantial difference. This finding aligns with the results of Li *et al*. (2013) and Li & Liu (2013), indicating that BME-BGS effectively promotes the continuous formation of fibrous connections at the fracture site, leading to the development of original callus and enhancing the efficiency of rehabilitation. In terms of clinical efficacy, the evaluation of patients in the Obs group showed 18 cases rated as “excellent”, 15 cases as “good”, and 2 cases as “poor”, resulting in a TER of 94.29 %. In the Ctrl group, the evaluation was “excellent” in 11 cases, “good” in 16 cases, and “poor” in 8 cases, with a TER of 77.14 %. It suggested that the TER of patients receiving BME-BGS was higher when compared with those treated by T-BGS. This indicates that compared to T-BGS, BME-BGS has a more pronounced therapeutic effect on patients and overall treatment efficiency is higher. Furthermore, the postoperative IOC of patients in the Obs group (11.43 %) was lower than 20 % in the Ctrl group, and a remarkable difference was observed. Postoperative complications refer to the occurrence of another or several diseases related to the treatment process of a certain disease. This indicates that BME-BGS can effectively reduce the risk of postoperative complications in patients, demonstrating its clinical safety.

CONCLUSION

The results of the present study revealed that compared to T-BGS, BME-BGS effectively reduced T-DFL of patients with DIBD after TF, promoted the secretion of osteogenic induction factors, and powerfully enhanced the efficacy of fracture healing, while maintaining clinical safety. It should be noted that this work was subjected to several limitations, including a relatively small sample size of only 70 patients from a single source. Furthermore, long-term prognostic data collection was lacking, which could potentially influence the conclusions. Therefore, future research will aim to include a larger number of TF patient cases, conducting multi-center comparisons of bone marrow enrichment surgical approaches. In conclusion, the findings of this work offer valuable insights for the clinical treatment of bone defect patients.

XU, Q.; WENG, H.; ZHU, L.; WU, M. & MEI, Z. Influencia del injerto óseo enriquecido con médula ósea frente al injerto óseo tradicional en la formación de callos y los factores de crecimiento óseo de pacientes con fractura de tibia y defecto óseo. *Int. J. Morphol., 43(3)*:759-765, 2025.

RESUMEN: Los defectos óseos constituyen un traumatismo ortopédico frecuente en la práctica clínica. La amputación de miembros se ha utilizado en el pasado, pero sus desventajas son evidentes. Los huesos autólogos son ampliamente reconocidos en la medicina moderna como el método de referencia para la fusión de injertos óseos debido a sus fuertes propiedades osteoinductivas, buena osteogenicidad y bajo costo. Fueron asignados aleatoriamente setenta pacientes diagnosticados con defecto óseo infeccioso distal (DOID) tras una fractura de tibia (FT) a un grupo de observación (Obs) (n = 35) y a un grupo de control (Ctrl) (n = 35). Se realizó cirugía de injerto óseo enriquecido con médula ósea (EMO-CIO) y cirugía de injerto óseo tradicional (CIO-T) en los grupos Obs y Ctrl, respectivamente, para comparación. El tiempo para la desaparición de la línea de fractura (T-DLF) y el tiempo para la consolidación de la fractura (T-FH) fueron considerablemente más cortos en el grupo Obs (P < 0,05). La puntuación de formación de callo postoperatorio (CPO), la proteína morfogenética ósea (PMO), el factor de crecimiento transformante (FCT)-β y los niveles del factor de crecimiento de fibroblastos alcalinos (CFA) en el grupo Obs fueron marcadamente más altos (P < 0,05). Además, la tasa de efectividad del tratamiento (TET) en el grupo Obs fue considerablemente más alta (P < 0,05). Mientras tanto, la incidencia de complicaciones (IC) en el grupo Obs (11,43 %) fue superior al 20 % en el grupo Ctrl (P < 0,05). En comparación con la CIO-T, la EMO-CIO puede acortar eficazmente el T-DLF en pacientes con DOID después de FT, promover la secreción de factores de inducción osteogénica y la formación de callos, y mejorar eficazmente la eficacia de la consolidación del extremo de la fractura, con seguridad clínica.

PALABRAS CLAVE: Defecto óseo; Fractura tibial; Formación de callos; Cirugía de injerto óseo enriquecido con médula ósea; Factor de crecimiento óseo.

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