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Application of Injectable Calcium Phosphate Cement with rhBMP-2 in the Elder Patients with Tibial Plateau Fractures

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Abstract
The tibial plateau fractures pose a therapeutic appeal. These fractures are often left with a large bone defect area after fracture reduction and articular surface restoration. Here we assessed the effect and safety of bone grafting with injectable calcium phosphate cement (CPC) with recombinant human bone morphogenetic protein (rhBMP-2) in 59 elderly patients with tibial plateau fractures. Fifty-nine tibial plateau fractures were treated by CPC with rhBMP-2 (experimental group) or CPC (control group) with open reduction internal fixation (ORIF). The difference between two groups in terms of Lane-Sandhu criterion and the function of the knee joint were compared. The mean period of follow-up was 14.2 months. All local incision had no itch sensation or pain. The experimental group average period of bone healing was 20.8 weeks, and the control group was 25.8 weeks. There was the obvious significant difference between the two groups in terms of Lane-Sandhu criterion. Moreover, the function of the knee joint was better. One year after an operation according to Rasmussen joint function grading. There was the obvious significant difference between the two groups ($P<0.05$). The mixture of Calcium phosphate cement with recombinant human bone morphogenic protein (rhBMp-2/CPC) is safe, convenient, and has less complications. The combination of material has better support for bone defect area after solidification and increases the safety of functional motion at an early stage. Meanwhile, rhBMP-2/CPC can be the suitable bone substitutions for a bone defect in elderly patients with tibial plateau fractures.
Keywords: calcium phosphate cement, bone morphogenic protein-2, bone substitution, tibial plateau fractures.

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1. Introduction

Tibial plateau fracture is common in the clinic, belonging to the intra-articular fractures affecting the weight bearing articular surface, which often result in compression, collapse, and splitting of the tibial plateau. Improper surgery often leads to knee instability, traumatic arthritis, and other severe consequences. At present, the locking plate is used to reset the fractured and unstable fracture of the tibial plateau and achieved some satisfactory results [1,2]. However, the tibial plateau fractures are often left with a large bone defect area where fragments were impacted into the soft metaphyseal bone after fracture reduction and articular surface restoration. If the chondral fragment is not adequately stabilized, then these subchondral voids can cause secondary fragment displacement and loss of reduction. In order to avoid the loss of articular surface reduction and delayed healing of fractures, bone graft in bone defect is often necessary to provide the joints supports and eliminate bone defect and are still the gold standard. [3]. The gold standard of bone graft remains autogenous bone graft (autograft). The only autograft achieves the most desirable properties of a bone graft material, including osteoconduction (the matrix), osteoinduction (growth factors), and osteogenesis (osteoprogenitor or osteogenic cells) [4].

However, bone autografts need an additional surgical site, with potential associated morbidity, and are limited in quantity. Allografts circumvent some of the issues relative to autograft, but they present concerns as well, such as the risk of transmission of infectious disease [5]. Immunological reactions to the recipient, loss of biologic and mechanical properties due to their processing, increased costs and availability. Synthetic bone graft substitutes have been gaining popularity as viable alternatives for void and defect filling eliminating the concerns with autograft and allograft. The synthetic bone graft substitutes currently available involve cements. These include calcium phosphate and/or calcium sulfates, hydroxyapatite, tricalcium phosphate, or combinations with rhBMP-2 thereof. Recent generations of bone substitutes have introduced the potential for synthetic bone grafts to promote biologic repair, and to provide support for treatment, such as antibacterial or bone morphogenetic proteins [6]. Recombinant human bone morphogenetic protein-2 is a soluble, local-acting osteogenic factor capable of causing the whole series of bone formation following implantation at ectopic (nonosseous) sites [7]. Although rhBMP-2 delivered in a buffer has been describing to speed up bone healing in several animal models, optimal bone formation seems to necessitate a carrier matrix [8-9]. Carriers uphold the concentration of BMP at the repair site for an adequate time period to allow bone-forming cells to move to the site of repair, proliferate and then differentiate in response to the BMP. Carriers can also provide an osteoconductive matrix and impart handling properties required for injection or implantation at the repair site. BMP carriers should necessarily possess a proper duration and compression resistance to maintain a space in which regenerative tissue formation can occur, in order to cause bridging of segmental defects. Different types of animal models were treated with an array of BMP-carrier combination to induce bridging of segmental defects [10].

In the minimally invasive procedure, the use of the majority of these BMP-carrier is prevented for surgical implantation. Additionally, when delayed administration of BMP is required after the previous surgery to increase the healing rate or when soft-tissue preclude adequate initial treatment, a second open surgical procedure is needed. An injectable BMP-carrier combination is possibly advantageous in surmounting these restrictions. It has been attested in few study that rhBMP-2 delivered in injectable calcium phosphate cement can speed up the healing of osteotomy sites in several animals [11,12]. In the present study, we evaluated the efficacy of rhBMP-2 delivered in an injectable calcium phosphate cement to achieve bridging of critical-sized defects in the elderly patients with tibial plateau fractures.

2. Materials and methods

2.1 Clinical materials

Fifty-nine patients with tibial plateau fractures were treated from January 2011 to December 2013 in the Affiliated East hospital of Tongji university, Shanghai, China. 32 patients in injectable rhBMP-2/CPC group (experimental group), included 15 males, 17 females, aging from 64 to 75-year-old with the average of 70.4 years; 27 patients in pure CPC group (control group) included 12 males, 15 females, aging from 62 to 72-year-old with the average of 68.3 years. The causes of injuries are described as follows: 32 cases in traffic injury, falling injuries divided into two groups which included 19 cases in simple falling injury and 9 cases in high falling injury. 50 cases of closed fractures and 9 cases of opened fractures, which are all Gastilolo type II. X-ray imaging and CT film were used in all the cases. According to Schatzker tibial plateau fracture classification, there were 16 of Schatzker II, 13 cases of Schatzker III, 12 cases of Schatzker IV, 10 cases of Schatzker V, and 8 cases of Schatzker VI, the time from the injury to the operation is 3.5h to 8d, there was no obvious difference in age, gender, and type of fracture between the two group ($p>0.05$)

2.2 methods

After lumbar or general anesthesia, the patients were placed in supine position, tourniquets were used in all the cases. All patients had deformation of the tibial plateau of more than five millimeters required reduction and fixation as well as impacted chondral fragments, which would result in subchondral cancellous bone defects after reduction. Limited specific exposure of the fracture site was used with open reduction. Depressed fragments were elevated to the anatomic joint line using a bone tamp, and preliminary fixation was achieved with thin Kirschner wires.

According to the amount of intraoperative tibial plateau bone defect, firstly, the curing liquid and powder of injectable calcium phosphate cement in a clean container were mixed in the proportion of 3 to 4g powder in 1ml, then rhBMP-2 powder was added, rhBMP-2 powder and CPC powder ratio was 2mg:1g, and uniformly mixed into a paste. The bone defect was intensively rinsed with sterile cooled Ringer's lactate, all blood clots and cancellous bones were removed. The mixture of rhBMP-2 and CPC is filled in the 20ml syringe and injected into the bone defect area through the fracture gap, so as to avoid leaving voids. Dry gauze was used to cover and compress the shape of the bone defect for 15 to 20 minutes until hardening of the material. After the artificial bone was completely hardened, holes were drilled and the screws or plates were placed according to the procedure. Antibiotic is given preoperatively and postoperatively in the cases of closed fracture, whereas in the open fracture the patients were treated with antibiotic 3 days postoperatively. In the control group, the prepared injected calcium phosphate cement is modulated into a paste and directly injected into the bone defect area, without adding rhBMP-2.

3. Results

3.1 Fractures healing

All cases were followed up for 10-22 months, an average of 14.2 months. No toxic effect, skin rash or high fever were found in all patients. Liver and kidney functions, blood routine, urines tests, and C-reactive protein were all normal. During follow-up, no occurrence of osteomyelitis, fractures, obvious collapse after bone defect repair was observed; no plate and screw loosening or other complication. During the follow-up, we observed in the experimental group, 8 to 10 weeks post-operation the absorption of injectable rhBMP/CPC began to appear. 12 to 14 weeks post-operation, a partial absorption was achieved, 16 to 18 weeks post-operation the absorption of most of the material was achieved; at 21 to 25 weeks post-operation the material was completely absorbed and replaced by new bone with satisfactory bone defect repair. An average of 20.8 weeks to obtain bone healing, no bone nonunion and neither bone infection occurred. In the control group the absorption of calcium phosphate cement started from 9 to 12 weeks' post-operation; partial absorption was observed from 12 to 15 weeks post-operation; from 17 to 20 weeks post-operation absorption of most of the material was achieved; 22 to 27 post-operation bone cement was completely absorbed and replaced by new bone with satisfactory repair of the bone defect. Same as in the experimental group, no bone nonunion and neither bone infection occurred. All the patients in the experimental group and the control group were compared separately at 1 month, 3 months, 6 months, 9 months and 12 months post-implantation. We evaluated the fracture healing, rhBMP-2/CPC complex and pure CPC injection with bone fusion, biodegradation substitution. The continuous comparison of X-ray image was made based on the Lane-Sandhu X-ray scoring criteria, included bone formation, bone connection, bone shape, 3 aspects which comprised 11 items: a) bone formation aspect: 0 point means no bone formation, 1 point means bone formation occupied 25% of the bone defect, 2 points means bone formation occupied 50% of the bone defect, 3 points means bone formation occupied 75% of the bone defect, 4 points means bone formation completely occupied the bone defect; b) bone connection : 0 means fracture line is visibly clear, 2 points means existence of some part of the fracture line, 4 points means fracture line totally disappeared; c) bone shape: 0 point means no born shape is seen, 2 points means the formation of bone marrow cavity, 4 points means cortical bone shaping. the scores of the three aspects were statistically analyzed.

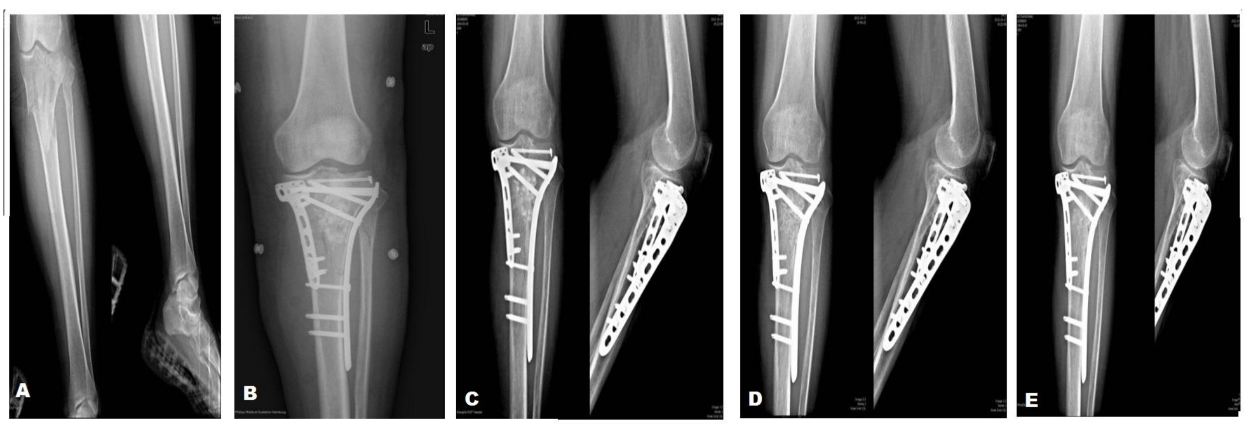

Figure1: X-ray (A) tibial plateau Schatzker type VI fracture (B) 1 week after operation showing filling of rhBMP-2/CPC (C) 12 weeks after showing partial absorption of rhBMP-2/CPC (D) 16 weeks after operation showing majority absorption of rhBMP-2/CPC (E) 22 weeks after operation shows total absorption of rhBMP-2/CPC.

3.2 Knee function

Post-operation knee function was evaluated by using Rasmussen knee function score system for evaluation. A total of 100 points, including 35 points for pain, 30 points for function, 30 points for a range of activity, 10 points for the anatomical position. Excellent: more than 90; good: 80 to 89 points; fair: 70 to 79 points; poor: less than 70 points. The Rasmussen scores of all patients at 6 months postoperatively are shown in Table 1 and 2.

4. Discussion

Fracture of tibial plateau belongs to the intra-articular fractures, is a clinically common fracture but difficult

Table 1: Comparison of Lane-sandhu X-ray score between the two groups after operation & follow up.

Group	1 month	3 months	6 months	9 months	12 months
Experimental	2.3 ± 1.61	4.5 ± 2.13	8.5 ± 1.26	10.8 ± 1.91	11.5 ± 2.21
Control	1.9 ± 2.37	3.1 ± 1.39	6.2 ± 3.21	8.5 ± 2.24	10.9 ±1.51
P value	0.137	0.043*	0.028*	0.037*	0.164
Note: * p< 0.05 statically significant					

Table 2: Comparison of Russmussen Knee function between experimental group & control group.

Group	Rasmussen	function	pain	Range of motion	Anatomical fracture
Experimental	91.3 ± 6.3	26.5 ± 4.4	30.1 ± 1.8	22.4 ± 2.8	7.1 ± 1.2
Control	89.8 ± 4.2	25.7 ± 4.1	29.2 ± 3.1	19.4 ± 7.3	8.2 ± 0.9
P value	0.396	0.081	0.872	0.046*	0.924
Note: * p< 0.05 statically significant					

To deal with it, often accompanied by the compression, collapse, and splitting of the tibia plateau. The tibial plateau fractures can be treated surgically and non-surgically. However surgical treatment for tibial plateau fractures can lead to many complications. Improper reduction often leads to serious consequences including knee instability, joint degeneration or traumatic arthritis [13,14]. If the tibial plateau fracture of the articular surface "step's greater than 3 mm, valgus instability is greater than 5 degrees, and there is a surgical indication for open reduction [15].

The principles of operation are fracture anatomical reduction, restoration of the articular surface of the knee and the axial alignment and stability of the internal fixation based on the early activities of the knee [16,17]. Due to anatomical features, after anatomical reduction of the tibial plateau fracture, often in the proximal tibia, the residual large bone defect at the site of the compression and collapse, can cause the articular surface that has been reset to be unable to get support and easily lead to a loss of the tibial plateau reduction.

In addition, it can also cause loose or fall off the internal fixation and other complications. Therefore, patients with larger bone defects should be treated routinely with bone graft during operation in order to prevent the re-collapse of the articular surface, it is beneficial to the stability of internal fixation. At the same time, bone graft can fill the cavity formed by bone defects to prevent hematoma formation, reduce the incidence of infection. Intraoperative bone graft has become a conventional treatment of tibial plateau fractures.

At present, the methods and materials for bone graft are varied. Autologous bone graft is considered as the gold standard of bone graft, but the bone mass is limited, and there are additional injuries and complications such as chronic pain wound infection and increased intraoperative blood loss. Although there is a wide range of sources about allogeneic bone and xenogeneic bone grafts, but there are immune rejection and low fracture healing rate and other shortcomings, which are limiting their clinical application. Studies have shown that transplantation of autologous cancellous bone, which is rich in cell and osteoinductive factors, is still a porous structure that plays a key role in osteogenesis and healing, which leads to a rapid vascularization [18]. Therefore, the bone cement produced should have a porous structure similar to autogenous bone.

In recent years, the clinical application of inorganic calcium salt artificial bone represented by CPC has been widely used. CPC can solidify itself in a short period of time at the ambient temperature, possesses the biodegradable property of bone conduction activity, the amount heat released during the solidification process is small, and the degradation of CPC in vivo can be gradually covered by autogenous bone [19]. As calcium phosphate cement has good bio-safety and tissue compatibility, it is widely used in the clinical practice of bone cement transplant material [20-22]. In clinical applications, the traditional bone cement needs to be performed into a certain shape in order to be completely used in the surgery, and cannot be completely filled with bone defects. Therefore, the technic of clinical application of injectable CPC is invented. Injectable CPC does not require early molding, the minimally invasive injection method can be used, it has the ability to completely fill the bone defects, and can be quickly solidified into porous microstructure scaffold materials, additionally plays the role of bone conduction *in vivo*.

Bone morphogenetic Protein-2 is currently recognized as the strongest inducer factor and is the key factor in controlling the signal pathway of fracture repair [23-26]. Recent studies have shown that rhBMP-2 can up-regulate the expression of vascular endothelial growth factor in osteoblasts and promote the proliferation of vascular endothelial cells, and has a strong role in promoting blood vessel growth [27-29]. However, the rhBMP-2 alone is susceptible to fluid dilution, protease degradation, and multiple problems such as inappropriate fixation of implants, which influence the effects of its osteoinductive activity. A large number of studies have shown that inorganic calcium phosphates have good affinity with BMP. Some studies have demonstrated the befits of CPC and rhBMP-2 mixture, which preserves the advantage of CPC and then offset the deficiencies of rhBMP-2 when used individually such as the osteoinductive activity that rhBMP-2 can't exert when used individually [30]. As a carrier of autologous bone substitute material, CPC is more favorable for the adsorption and growth of cells because of its rich porous structure, which assists the rhBMP-2's osteogenesis effect to culminate in a better achievement. The metabolite of rhBMP-2 / CPC is nano-type bone apatite, with low crystallinity, good biocompatibility, strong plasticity and little volume change [31].

We experienced in clinical practice, concerning the tibial plateau fractures that cause irregular bone defect area, when we adopt the conventional use of granular or long bone cement filling, we found out that it is difficult to fill the bone defects in every corner, it cannot completely fill the bone defects, which may affect the reconstruction process of the tibial plateau conduction frame structure, and prolong the healing time of the fracture. The injectable rhBMP-2/CPC does not only compensate the failing of the bone defect filling but can be injected in multiple directions from the original fracture gap, without needing another slot or shearing bone, the influence of the disturbance of blood supply in fracture area is small, this can fill the void and bone defect zone that were created after the fracture reduction, provide a good biological basis for fracture healing, and the induction activity of rhBMP-2 has a strong preventive effect on postoperative nonunion and delayed healing.

After follow-up of the fracture healing in this group, we observed that the absorption of injectable rhBMP-2 / CPC started to be seen 8 to 10 weeks after surgery; partial absorption occurred 12 to 14 weeks after surgery; total absorption occurred 16 to 18 weeks after surgery, Bone density is comparable to the surrounding cancellous bone; 21 to 25 weeks after bone cement is completely absorbed and replaced by new bone, there was a satisfactory bone defect repair. Therefore, within 10 weeks after surgery, avoidance of lifting heavy weights or manual labor, which help to prevent re-displacement of the fracture and loosening of the internal fixation. Due to the degradation of rhBMP-2 / CPC and bone regeneration are basically synchronous, if the bone cement is absorbed in the following 3-6 months, the X-ray film does not show callus formation, nor should we have to worry about its stability, the effective functional exercise can still be carried out, in addition to the Rasmussen functional score, activity of the experimental group was significantly better than the control group, and $P < 0.05$, indicating that the difference was statistically significant. We believe that after the use of BMP-2 in the experimental group, the extensive vascularization of bone fracture and osteoinduction that increase the rate of the fracture healing and shorten the recovery time may be beneficial for patients to perform the earlier postoperative functional exercises, and prevents joint tissue adhesion and the joints stiffness from occurring.

The X-ray films of the experimental group and the control group were evaluated at one month, 3 months, 6 months, 9 months and 12 months by Lane-Sandhu X-ray scoring respectively. It showed that 3 Month, 6 months and 9 months after operation, the bone formation, bone degradation and replacement were significantly better in the experimental group than in the control group, and there was significant difference between the two groups in the statistical analysis, which objectively illustrated the injectable rhBMP-2/CPC Bone cement in the treatment of intra-articular fractures is superior to the use of CPC artificial bone graft.

5. Conclusion

In conclusion, rhBMP-2 / CPC can be used to treat tibial plateau fractures with high early strength and good replacement of bone cement, which can improve the early functional exercise of the knee joint. Because rhBMP-2 and rhBMP-2 can be filled completely and tightly, rhBMP-2 / CPC can improve the tight connection of fracture ends, promote the healing process of fracture and reduce postoperative nonunion and delayed union of the fracture. It is one of the best methods to fill the bone of tibial plateau.

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