A novel type of bone cement, magnesium potassium phosphate cement (MKPC), was fabricated by mixing 5% phosphoric acid with magnesia, potassium dihydrogen phosphate, sucrose, hydroxyapatite, and sodium tri-polyphosphate powders. The surface morphology and mechanical strength of MKPC were investigated together with tissue responses following implantation into rabbit condylar defects, using commercially available calcium phosphate cement (CPC) as the control. The results showed that MKPC had a higher compressive strength (25.40 ± 0.61 MPa) than CPC (16.45 ± 1.91 Mpa) and did not initiate foreign body reaction, inflammation, or necrosis in vivo. Both cements were resorbed by creeping substitution, in which the resorbed cement was replaced by the newly formed bone. MKPC had a higher resorption rate and enhanced bone regeneration compared to CPC. The data presented here indicate that MKPC could be a potential bone void filler for bio-adhesion in clinical applications.

Abstract: A study on bone cement containing magnesium potassium phosphate for bone repair

1. Introduction
Irregular bone defects and unstable fractures (particularly comminuted fractures due to osteoporosis) frequently occur in clinics and are difficult to cure (Habibovic & Groot, 2007). For massive bone fractures, the main treatment methods in clinics include incision restoration with internal fixation, microplate screw fixation, and intramedullary fixation (Yu et al., 2010). However, fixation of small bone fractures is a challenge for orthopedic surgeons. Even in massive bone fractures, the fixation is not easy because the spongy bone makes the fixation ineffective due to its weaker...
mechanical strength. In such cases, postoperative slippage frequently occurs, and a secondary operation is often necessary (Weninger et al., 2009). In response, scientists developed bone cements to attach various objects together in bone fractures and regenerate bone in bone defects. Bone cements are mainly composed of bioactive calcium phosphates or relatively bioinert polymers such as polymethylmethacrylate (PMMA).

Calcium phosphate cement (CPC) has been used for more than three decades. Paste or injectable CPC has the advantage of being freely moldable and adaptable to bone defects (Zhang et al., 2012). The combination of high biocompatibility, ease-of-shaping, and the capacity for self-setting under ambient conditions makes CPC a useful bone filler material (Barbieri, Yuan, Groot, Walsh, & Bruijn, 2011; Carey, Xu, Simon, Takagi, & Chow, 2005; Palmer et al., 2016; Tien, Chih, Lin, Ju, & Lin, 2004). However, the high molar ratios of Ca and P make CPC poorly resorbable and not highly adhesive (Jansen, Ooms, Verdonschot, & Wolke, 2005). In 2004, the FDA released warnings of serious compression from using CPC to treat compression fractures of the spine. PMMA is an acrylic bone cement, which has been used for plate luting and total arthroplasties for almost 50 years (Hirvinen, Litsky, Samii, & Weisbrode, 2009; Smith, 2005). Unfortunately, PMMA releases considerable amounts of heat during the curing process and causes cell death in the surrounding bone tissue. Furthermore, the resulting materials shrink during the setting of PMMA, which causes poor resistance to fractures. Moreover, PMMA is not very resorbable and is less biocompatible due to the release of a toxic monomer into the blood stream (Hirakawa, Jacobs, Urban, & Saito, 2004; Kuehn, Ege, & Gopp, 2005). Additionally, PMMA is bioinert; there is little evidence that PMMA promotes significant new bone formation.

Recently, an adhesive material, magnesium phosphate cement (MPC), has attracted attention as a potential biodegradable bone implant material (Liu; Waselau, Samii, Weisbrode, Litsky, & Bertone, 2007; Yu et al., 2010). The main components of MPC are magnesia (MgO, dead-burnt) and ammonium dihydrogen phosphate (NH₄H₂PO₄), which react with water to form ammonium magnesium phosphate (MgNH₄PO₄) as the final product (Liu, Kumar, Kwag, & Ra, 2013; Masuda, Ogino, & Mukai, 2013). Compared with CPC, MPC has the advantages of rapid setting and higher initial mechanical strength (Mestres & Ginebra, 2011; Wang et al., 2013). However, the release of NH₃ from the final product of MgNH₄PO₄ into the physiological environment generally causes cytocompatibility issues (Demeestere, Smet, Van Langenhove, & Galbacs, 2001). To improve MPC, the MKPC, consisting of magnesia (MgO, dead-burnt) and potassium dihydrogen phosphate (KH₂PO₄) and with potassium magnesium phosphate (MgKPO₄) as the final product, has been developed (Li, Ji, Huang, Xu, & Yan, 2017). MKPC has a controlled exothermic reaction lower than approximately 50°C, is easy to work with, has flexible working time, and is easily injected using a syringe; therefore, MKPC has potential multipurpose applications as a bone graft, filler, adhesive, binder, anchor, and cement. However, the high concentration of K⁺ and Mg²⁺ in MKPC may cause cell death, indicating potassium dihydrogen phosphate and magnesia cement are not optimal for clinical applications. By introducing chelating agents into MKPC, we developed a novel type of MKPC that decreases the excess K⁺ and Mg²⁺ (Zhang et al., 2016).

In this study, the novel MKPC was compared with a commercially available CPC in rabbit condylar bone defects up to 26-week implantation, with respect to bone regeneration and material resorption.

2. Materials and methods

2.1. Preparation of MKPC
MKPC powder consists of 43% MgO (dead-burnt) (Xingtai Metallurgical Magnesium Industry Co., Ltd.), 43% KH₂PO₄ (Hunan Jiudian Pharmaceutical Co., Ltd, China), 4% sucrose (Hunan ER-KANG Pharmaceutical Co., Ltd, China), 8% hydroxyapatite (HA) (Engineering Research Center in Biomaterial, Sichuan University, China), and 2% sodium tri-polyphosphate (Chengdu Chron Chemicals Co., Ltd, China) by weight. MgO was obtained by heating magnesium carbonate...
pentahydrate at 1500°C for 6 h. The cement liquid was 5% phosphoric acid solution (Hunan ER-KANG Pharmaceutical Co., Ltd, China). The MKPC pastes were made by mixing MKPC powder (particle size < 45 μm) with cement liquid in a proportion of 10:3 (mass/volume ratio, g/mL). To characterize the properties of MKPC, MKPC paste was loaded into a stainless-steel mold and stored at 37°C in a 100% humidity box for setting for 24 h. For animal studies, the cement was prepared prior to implantation and loaded as a paste into bone defects. CPC (Shanghai Rebone Biomaterials Co., Ltd, China) was used as a control and was prepared according to the manufacturer's instructions.

2.2. Characterization of the MKPC cement
The fractured surface of the MKPC samples was examined using scanning electron microscopy (SEM; JSM6360, JEOL, Japan), and the chemical composition of the MKPC was identified using X-ray diffraction (XRD; Miniflex II, Rigaku, Tokyo, Japan).

The compressive strength of the MKPC and CPC scaffold (10 × 10 × 10 mm) was measured at room temperature using an MTS-858 Mini Bionix biomechanical testing machine (MTS Systems Corp. Eden Prairie, MN, USA) at a constant displacement rate of 2 mm/min. Three replicates were performed three times for each group (n = 3), and the results were expressed as the means ± standard deviation (mean ± SD).

2.3. In vivo experiments
The study was performed with the permission of the local animal care committee (Animal Center, Sichuan University, Chengdu, China). Twenty-four healthy female adult New Zealand rabbits, about 1 year old, with average body weight 3.0 kg, were chosen as models for studying the bone regeneration potential of MKPC in femoral condyles. General anesthesia was induced with an intravenous injection of 3% sodium pentobarbital (1 mL/kg).

To eliminate errors of different animals, the MKPC and control sample CPC were implanted in the same rabbit. Critical size defects (Giavaresi et al., 2010) (6 mm diameter, 10 mm length) were transversally created in the femoral distal epiphysis by a standardized surgical procedure (Figure 1a). A 3-cm skin incision was made on the lateral aspect of the distal femoral condyle, muscles were separated, and the femoral condyle was exposed. Cancellous defects were stepwise drilled with a 3.0-mm globular drill and subsequently expanded with a 6.0-mm drill. The depth of the defects was 10.0 ± 0.5 mm, as measured using a digital caliper. The bone cavities were washed three times.
with physiological saline to eliminate bone debris and dried with gauze. The defects were randomly filled with either MKPC or CPC (Figure 1b). The incision was sutured in a layered fashion. The animals were housed separately. Each rabbit received 4.0 × 10^6 units of penicillin intramuscularly, once a day, for three successive days. All rabbits were fed standard granulose food, free moving. To monitor bone formation over time, 5 mg·kg^{-1} body weight calcein (Sigma), 50 mg·kg^{-1} body weight xylene orange (Sigma), and 20 mg·kg^{-1} tetracycline-HCl (Sigma) were intravenously injected at 3, 6, and 9 weeks after implantation, respectively, for the 12-week implantation in animals. Rabbits were sacrificed at the day of surgery, and 4, 12, and 26 weeks post-surgery. Six rabbits (12 limbs) were allocated for each time point.

2.4. Evaluation of bone regeneration

2.4.1. Gross observation
Postoperative diet, body weight, activity, wound reaction, and binding between bone graft and host bone were observed.

2.4.2. Radiographic observation
Bone regeneration was evaluated on the day of surgery and at 4, 12, and 26 weeks post-surgery using plain radiograph.

2.4.3. Histological analysis
The bone defect region was considered the center, and 2.5 cm of femurs were resected and all soft tissue was removed. Then, samples were fixed in 4% paraformaldehyde, followed by dehydration with a series of ethanol and embedded in PMMA. Non-decalcified sections (10–20 µm) were cut with a histological diamond observed and stained with 1% methylene blue (Sigma-Aldrich) and 0.3% basic fuchsin (Sigma-Aldrich, Missouri, USA) for histological observation and histomorphological analyses. For fluorochrome labeling (12-week samples), non-stained sections were prepared for fluorescent observation. Finally, the sections were observed under a light microscope for signs of degradation of implanted material and bone formation or florescence microscope for the metabolism of bone surrounding the implants.

2.4.4. Histomorphometrical analysis
To quantitatively determine the resorption of cement implants, sections crossing the middle of the implants (the section 5-mm deep from the lateral condyle surface) were subjected to histomorphometry. Histological overviews of the stained sections were first generated with a slide scanner (Dimage Scan Elite 5400 II, Konica Minolta, Japan). Quantitative histomorphometry was performed using Adobe Photoshop software (CS4, Adobe Systems Benelux BV, Amsterdam-Zuidoost, and the Netherlands). Pixels of the cement materials (M), pixels of the defect (Ø6.0 mm, region of interest, ROI), and the bone in the defects (B) were read. Material percentage (M% = M × 100/ROI) in the defect and bone percentage [B% = B × 100/(ROI-M)] was then calculated. A total of six samples were available per material per time points of 0, 4, 12, and 26 weeks. The material percentage and bone percentage in the defects were presented as the mean ± standard deviation (mean ± SD).

2.5. Statistical analysis
Results are expressed as the mean ± standard deviation (mean ± SD). Comparative studies of means were performed using one-way ANOVA followed by a post hoc test (Fisher projected least-significant difference) with statistical significance at p < 0.05.

3. Results

3.1. Characterization of MKPC
The XRD pattern of hardened MKPC cement is shown in Figure 2. According to the diffraction peaks, there are two elements in the MKPC; one element is unreacted magnesium oxide. The other element is MgKPO₄·6H₂O (MKPC), commonly called struvite of potassium. According to
the JCPDS system, the JCPDS card number for MKPC is 35–0812, and the characteristic peaks are $d = 4.241$, 2.899, and 4.123 nm. The MKPC is not only a crystal form but also exists as an amorphous form. Therefore, mainly diffused diffraction peaks exist around the main diffraction peaks (Ding, Bq, Xing, Ng, & Zj, 2012; Regy, Mangin, Klein, & Lieto, 2002).

SEM imaging showed that the microstructure surface of MKPC comprised small grains (approximately 1–3 μm) and numerous microspores with sizes ranging from 0.8 to 3.0 μm (Figure 3b). The microstructure surface of the CPC formed a powder-like structure with much larger pores (5–10 μm) (Figure 3a). The compressive strength of MKPC reached 25.40 ± 0.61 Mpa, whereas the control sample CPC was 16.45 ± 1.91 Mpa.

3.2. In vivo biocompatibility

3.2.1. Gross observation
After recovery, all rabbits presented with normal diet and good mental status, the body weight changes of rabbits after operation are shown in Table S1. The inflammatory reactions, such as incision swelling and exudation, were not observed in this study. Neither inflammation nor necrosis was noted during sample harvesting at weeks 4, 12, and 26 post-surgery.
3.2.2. X-ray analysis
On the day of surgery, X-ray examination demonstrated that the femoral condyle defects were well filled with materials; the material and bone tissue had obvious boundaries (Figure 4a,e). The boundary disappeared with time. Defects became more transparent in X-ray plain radiographs (Figure 4), and this trend was clearer in the case of MKPC (Figure 4e–h) than CPC (Figure 4a–d).

3.2.3. Histological evaluation
Histological analysis of MKPC implanted into the bone defects of rabbit femoral condyles is shown in Figure 5e–h and Figure 6e–h. On the day of the surgery, the margins of materials and bone tissue are clear and smooth. At 4 weeks after surgery, the MKPC was encapsulated by bone tissue, and the MKPC sample started to degrade from the edge of the material. After 12 weeks, new bone
was formed and grew into the pores; resorption of MKPC was evident on the margin materials. After 26 weeks, the resorption of MKPC continued and paralleled the new bone formation.

The histological analysis of control material CPC scaffolds implanted in the bone defects of rabbit femoral condyles was also performed (Figure 5a–d and Figure 6a–d). Bone was formed on the CPC surface at week 3, and resorption of CPC rarely occurred in 4 and 12 weeks.

Fluorescent microscopic observation showed bone formation on the implant surface of both MKPC and CPC at week 3 (Figure 7, green color). Normal bone metabolism was seen in bone defects with both MKPC and CPC, as indicated by the bone formation at week 6 (red color) and week 9 (yellow color).

3.2.4. Histomorphometrical analysis
The percentage of newly formed bone and the presence of materials in the defects are shown in Figure 8. The amount of newly formed bone in the defect area increased with time, whereas the material percentage decreased. At 26 weeks after implantation of MKPC, the amount of newly formed bone was 29.6% for MKPC (Figure 8B), and 37% of MKPC was resorbed (Figure 8A). At 26 weeks after implantation of CPC, the amount of newly formed bone was 15.8%, and 80% of the material remained in the defects. The results indicate that the percentage of newly formed bone area for MKPC is significantly higher than that of CPC at 26 weeks ($p < 0.05$).

4. Discussion
Both CPC and MKPC are handled as a paste and are easily injectable, while MKPC allows possibilities in adjusting the setting time, degradability, and bioactivity (Dai et al., 2014). The main chemical reaction of MKPC is an acid–base reaction of MgO and KH$_2$PO$_4$, with MgKPO$_4$·6H$_2$O as the final reaction product. The chemical reaction equation was MgO + KH$_2$PO$_4$ + 5H$_2$O $\rightarrow$ MgKPO$_4$·6H$_2$O (Qiao, Chau, & Li, 2012).
However, the excess of K$^+$ and Mg$^{2+}$ in MKPC is harmful for cells. As demonstrated in our previous study (Zhang et al., 2016), the cell proliferation rate in vitro for MKPC was 51.2%, and the cell proliferation rate increased to 119.6% after the excess K$^+$ and Mg$^{2+}$ were buffered with sodium tri-polyphosphate. Sodium tri-polyphosphate not only decreased the concentration of K$^+$ and Mg$^{2+}$, to which cells are sensitive, but also adjusted the osmotic pressure, which is important for cell survival. The osmotic pressure of MKPC alone (0.2 g MKPC in 1 mL cell culture medium, and incubation at 37°C and 100% humidity for 24 ± 2 h) was 450 mosm, whereas the osmotic pressure of MKPC with the addition of sodium tri-polyphosphate was 320 mosm (data not shown). As a chelating agent, sodium tri-polyphosphate reacts with excess K$^+$ and Mg$^{2+}$ (Andersen, Hägerstrand, & Nordberg, 1982); thus, the biocompatibility of MKPC is improved. As a result, the novel MKPC cement used in this study was biocompatible, with no foreign body reaction, and no inflammation and no necrosis observed. Biocompatibility was further enhanced by the use of MgO and KH$_2$PO$_4$. MgO was a type of oral antacid medicine of 400–840 mg dosage (Yu et al., 2010). KH$_2$PO$_4$ is commonly used as a pharmaceutical excipient. After hydration, MKPC is converted into potassium magnesium phosphate in vivo, which is the common biomineral existing in the body. Bone formation occurred on the MKPC surface directly without an intervening connective layer (Figure 6), indicating that the MKPC cement is bioactive. The bioactivity is because of the presence of HA (%) in the cement. Generally, and as shown in this study, cement (e.g., CPC) containing calcium phosphate is bioactive and allows bone formation on its surface.

The compressive strength of CPC (16.45 Mpa) was lower than that of MKPC. Because of its low mechanical strength, CPC disintegrated into small particles in the in vivo environment. For this reason, an FDA release warns of serious complications using existing CPC in treating compression fractures of the spine. The compressive strength of the MKPC cement after hardening for 24 h was significantly higher than that of CPC (25.40 MPa), and the cement remained intact in vivo. The high compressive strength of MKPC was attributed to two reasons. First, in the MKPC paste, a significant portion of MgO particles remained unreacted (Figure 2), and the MgO particle framework in MKPC could increase the mechanical strength of the cement body (Qiao et al., 2012). Second, the crystal products and MgO particles could constitute a cement framework that allows the crystal lattices to be filled with an amorphous mass, and an uninterrupted microstructure could be formed (Ding et al., 2012).

The novel MKPC cement was resorbable, although 70% cement body remained after 26 weeks. At 4 weeks, a clear degradation can be observed at the edge of the material. Both chemical dissolution (passive degradation) and cell-mediated resorption may occur in the resorption. Passive degradation came from the chemical nature of MgKPO$_4$·6H$_2$O, whereas the cell-mediated resorption was evident with the presence of osteoclast-like cells and resorption lacunae on the MKPC surface (Figures 5, 6). Furthermore, osteoclast-like cells and resorption lacunae on the MKPC surface indicated that MKPC was resorbed in vivo in a “creeping substitution” manner (Yuan, Li, Bruin, Groot, & Zhang, 2000). Because of the creeping substitution of MKPC cement, it could not be expected that the MKPC would rapidly disappear in vivo. The present study showed that the
The degradation rate of MKPC was higher than the control material CPC (Figure 8a). The high degradation rate of MKPC could be attributed to the rapid dissolution of MgKPO4·6H2O. The high molar ratios of Ca and P gave CPC a relatively low degradation rate (Jansen et al., 2005)

The degradation products (K+ and Mg2+) did not affect bone metabolism surrounding the implants, as shown in the fluorescent observation, and bone was formed in the defect in the tested time frame for both MKPC and CPC. Furthermore, the presence of Mg2+ stimulates osteogenesis (Janning et al., 2010; Landi et al., 2008; Tamimi et al., 2011), and bone regeneration was enhanced in the defects repaired with MKPC (Figure 8b).

To overcome the shortcoming of excess K+ and Mg2+ in the traditional MKPC, we introduced sodium tri-polyphosphate into the MKPC cement. This addition improved the biocompatibility of the resulting cement. Moreover, introducing HA into the cement made the novel MKPC cement bioactive. Compared to the commercially available CPC cement, the novel MKPC cement has a higher mechanical strength, a higher resorption rate, and enhanced bone regeneration.

5. Conclusions
A novel MKPC cement was evaluated in this study using the commercially available CPC as a control. The MKPC has stronger mechanical strength than the CPC control and does not cause foreign body reaction, inflammation, and necrosis in vivo, confirming its biocompatibility. Furthermore, MKPC allowed bone formation on its surface and thus is bioactive. Compared to the CPC control, MKPC was resorbed faster and enhanced bone regeneration. The overall results indicate that MKPC could be developed as a potential bone void filler and bio-adhesive for clinical applications.

Supplementary material
Suplemental material for this article can be accessed here https://doi.org/10.1080/23312025.2018.1487255.

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Competing Interests
The authors declare no competing interests.

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