A novel device for treatment of osteonecrosis of femoral head: Feasibility and preliminary efficacy of animal study

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ABSTRACT

Background: Interruption of blood supply will lead to necrosis of body tissues, such as osteonecrosis of femoral head (ONFH). Vascularization has always been regarded as one of the biggest challenges in tissue engineering. In the current study, a novel device was proposed to reconstruct blood supply of necrotic femoral head.

Methods: Cryo-insult with liquid nitrogen method was adopted to establish the ONFH model. In experimental group, a novel scaffold carrying vascular bundle was implanted into the necrotic femoral head after decompression and the transplanted vascular bundles were anastomosed with the existing blood vessels around the hip. In control group, a traditional porous scaffold was inserted alone without vessels. Feasibility of this strategy was verified by animal experiments. Micro-CT analysis and histological evaluation were performed to investigate its preliminary efficacy.

Results: Feasibility of this innovative treatment strategy had been successfully verified in animal experiments. In the area of necrosis repair, more bone tissue grew into the scaffold in experimental group than the control group evaluated by Micro-CT (three months: 29.66% VS 20.35%, P < 0.05; six months: 30.47% VS 25.10%, P < 0.05) and histological analysis (24.71% VS 16.45%, P < 0.05 at three months; 31.01% VS 20.60%, P < 0.05 at six months). Implanted vascular bundles had the potential to branch out many branches in the osteonecrosis repair area to facilitate blood supply reconstruction and bone repair.

Conclusions: This study proposed a novel device with clinical application prospects in the treatment of ONFH. It has the potential to provide new possibilities for rebuilding the blood supply of femoral head and repairing osteonecrosis.

Translational potential statement: The novel device proposed in this study has the potential to be applied to the treatment of early femoral head necrosis.

1. Introduction

As a highly vascularized tissue, the development, survival and regeneration of bone depend on its vasculature [1–4]. Destruction of vasculature in femoral head will lead to osteonecrosis of femoral head (ONFH). It can occur due to a variety of reasons. Corticosteroids use, for instance, is one of the most common causes [5–7]. Currently in global treatment of COVID-19 pandemic, the application of corticosteroids has been proven to be effective in reducing mortality rate of critically ill patients [8]. World Health Organization (WHO) also recommends systemic corticosteroids use for severe COVID-19 patients [9]. However, this may also make these patients face a higher risk of sequelae of ONFH,

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referring to the incidence of steroid-induced femoral head necrosis (24%) in the treatment of severe acute respiratory syndrome (SARS) which broke out in 2003 [10–12]. It is foreseeable that with global spread of COVID-19 pandemic and application of corticosteroids, the number of patients diagnosed with ONFH will also significantly increase in the near future. Although there are many hip preservation interventions to prevent disease progression in treatment of ONFH, effective reconstruction of blood supply in the femoral head is still a major challenge in clinical and scientific research. In the current study we proposed a novel method to reconstruct blood supply for the necrotic femoral head by implanting a newly designed scaffold as carrier of transplanted vascular bundles and vascular anastomosis. The feasibility and preliminary efficacy for treatment of ONFH was further investigated in animal study.

2. Materials and methods

2.1. Design and fabrication of novel/traditional scaffold

A novel device for treatment of ONFH was designed: porous titanium scaffold (pore size = 400 μm) with an internal U-shaped channel was designed as carrier of transplanted blood vessels in the experimental group (Porous titanium scaffold with vessels group, PTSV group, Fig. 1A). An open window was located on the side of top of scaffold (Fig. 1A) to ensure the successful insertion of vessels. The end of scaffold was designed as a solid structure with threads to achieve anchoring in cortical bone after implantation. Traditional porous titanium scaffold without U-shaped channel, open window or vessels was applied in the control group (porous titanium scaffold group, PTS group, Fig. 1B) to simulate the effect of tantalum rods used in clinical practice. Scaffolds were fabricated with Ti6Al4V power by selective laser melting method (SLM; Concept Laser, Lichtenfels, Germany). Parameters of scaffold were set according to the measurement results of proximal femur of sheep in preliminary experiment: diameter of porous part (8 mm) and thread part (10 mm), total length (41–50 mm) in both group; diameter of the U-shaped channel (2.5 mm). In PTSV group, the saphenous artery of the animal was taken as a graft vessel. The vascular bundle was implanted into the experimental scaffold under the protection of catheter and guide wire. Then, scaffold carrying vascular bundle was implanted into the necrotic femoral head after decompression and the two ends of the transplanted vascular bundle were respectively anastomosed with the branches of the lateral femoral circumflex artery and vein to form an arteriovenous loop (Fig. 1A). In PTS group, scaffold was inserted alone without vessels (Fig. 1B).

2.2. Animal experiments

All procedures strictly followed international animal protection guidelines and were approved by the Institutional Animal Care and Use Committee of Fuwai Hospital (NO: 0080-2-30-HX(X)). Fifteen adult female Small Tailed Han sheep (age 24–36 months, weight 60–85 kg) were used in animal experiment. Cryo-insult with liquid nitrogen method was adopted to establish the ONFH model in right hind limb of sheep as previously described [13,14]. Briefly, after successful anesthesia, the surgical limbs were prepared and disinfected. Posterior side of femoral head–neck junction was exposed. A tunnel (3 mm in diameter and 12 mm in depth) was induced by drilling from head–neck junction towards the weight-bearing area of femoral head (Fig. 2A). A cryoprobe was then inserted into the tunnel to induce cryogenic lesion (Fig. 2B). The cryo-insult was conducted by three freeze–rewarm cycles. After sealing the tunnel with bone wax, the incision was closed with 3–0 sutures. Postoperatively, experimental animals could move freely without restriction.

Three animals were sacrificed, and bilateral femoral head were harvested to verify the reliability of this model through histological examination at one month postoperatively. The remaining twelve animals were randomly divided into two groups (n = 6 for each group) and received scaffold implantation procedure. In the PTSV group, after successful anesthesia, the surgical limbs were prepared and disinfected. A longitudinal incision was made on inner side of left hind limb. Saphenous artery over 20 cm was obtained as transplanted blood vessel following careful separation and ligation of the branches (Fig. 3A/B). Under protection of catheter, the transplanted saphenous artery was transferred into the novel scaffold with U-shaped channel for future use (Fig. 3C). An arc incision was made in front of greater trochanter of the right hind limb and the cortex at base of greater trochanter was exposed by separation. Under fluoroscopy, a guide needle was implanted into the necrotic area through lateral cortex, and a hollow drill with the same diameter as scaffold was used to remove the necrotic bone in femoral head to prepare the core decompression channel for scaffold implantation. Vastus lateralis was detached from its origin of greater trochanter and retracted distally to expose transverse branch of lateral femoral circumflex artery and its accompanying veins. The experimental scaffold carrying transplanted vessel was then inserted into core decompression channel, ensuring that the top window faced downward (Fig. 1A). Finally, the two ends of graft vessel were anastomosed with transverse branch of lateral femoral circumflex artery and its accompanying vein (Fig. 3D). The pulsation and patency of anastomosed blood vessels were checked again before closing the wound in anatomical layers. Cefazolin (50 mg/kg) was administered intramuscularly during surgery preparation and 3 days after surgery (twice a day) for prophylactic use. Papaverine and low molecular weight heparin were used for three days after operation to prevent arterial crisis and thrombosis. In PTS group (control), after elimination of necrotic bone and preparation of core decompression channel, traditional porous scaffold was directly inserted without vessels. Animals were sacrificed for imaging and histological evaluation at three and six months after surgery.

2.3. Micro-CT analysis

Samples of proximal femur were retrieved and fixed in 4% paraformaldehyde solution. Specimens were scanned by Siemens Inveon Micro-CT/PET (Siemens, Berlin, Germany). Resolution of 10 mm, Voltage of 60 kV, Current of 400 mA). Images were reconstructed and analyzed with Inveon analysis workstation. To evaluate bone ingrowth of implanted scaffolds, the scaffold area (top side, 15 mm in height) was selected as region of interest (ROI) for Micro-CT analysis. Bone tissue was separated from high-density titanium scaffold by using the threshold function.

2.4. Histological evaluation

After Micro-CT analysis, proximal femur samples were further cut along head–neck junction to obtain femoral head for subsequent histological evaluation of bone and vascular ingrowth. Femoral head were

![Fig. 1. A: a novel method to reconstruct blood supply for the necrotic femoral head by implanting a porous scaffold as carrier of transplanted vascular bundles and vascular anastomosis in PTSV group. B: Traditional porous scaffold inserted alone without vessels in PTS group.](image-url)
embedded in methyl methacrylate after dehydrated in a graded ethanol solution. Specimens were cut along coronal plane of femoral head by using Leica Microtome (Wetzlar, Germany). Sections were further stained with Von-Gieson staining or toluidine blue staining. Since it was the top of scaffold which replaced original osteonecrotic area, we selected this part (top side, 5 mm in height) as the region of interest (ROI) in histological analysis. ImageJ software was used to calculate the percentage of bone volume (BV/TV) in ROI.

2.5. Statistical analysis

SPSS 20.0 software was used for statistical analysis. Student’s t-test was used to analyze the differences between groups. Statistically significant value was set as \( p < 0.05 \).

3. Results

3.1. Reliability of ONFH model

To evaluate reliability of ONFH model induced by cryo-insult,

femoral head samples were harvested for histological examination at one month after cryogenic intervention. Histological analysis showed most bone lacunae in trabecula of the normal femoral head were filled with deeply stained osteocyte nuclei (Fig. 2C), while the cryo-insult side was filled with many empty osteocyte lacunae (Fig. 2D), indicating the successful establishment of ONFH model.

3.2. Micro-CT analysis

During this experimental period, no obvious femoral head collapse was found in both groups. Micro-CT analysis showed significantly more bone ingrowth in PTVS group than PTS group at both three (29.66% VS 20.35%, \( P < 0.05 \)) and six months (30.47% VS 25.10%, \( P < 0.05 \)) after implantation (Fig. 4).

3.3. Histological evaluation

Von-Gieson staining was performed at three and six months after implantation to evaluate bone repair effect in both groups. Toluidine blue staining was conducted at six months after surgery to investigate
revascularization. Von-Gieson staining showed significantly more bone ingrowth in PTSV group than PTS group at both time points (24.71 ± 4.11% VS 16.45 ± 1.58%, P < 0.05 at three months; 31.01 ± 2.80% VS 20.60 ± 2.89%, P < 0.05 at six months) (Fig. 5). Newly formed bone tissue was mostly confined to the surface of the titanium column in PTS group, while the pores in scaffold of PTSV group had significantly higher filling rate of bone tissue (Fig. 5A). Toluidine blue staining showed that compared with traditional scaffold in PTS group, many branch blood vessels sprouted around the implanted vascular bundle in PTSV group, indicating better vascularization (Fig. 6).

4. Discussions

The dense blood vessels in skeletal system can provide a significant amount of blood supply, which is essential to maintain the structural and functional integrity of bone tissue [1,4]. Destruction of blood supply has been proven to be related to skeletal system diseases such as osteonecrosis [5,6], osteoporosis [15], and nonunion of fractures [16]. Due to the unique anatomical environment, femoral head is surrounded by synovial fluid. Its own blood supply is limited, which makes it a common site of osteonecrosis.

Various hip-preserving surgeries are used for the treatment of ONFH, such as core decompression [17–19], cell-based adjuvant therapy [20,21], tantalum rod implantation [22–24], autologous/allogenic graft [5,6]. However, tantalum rods or other grafts usually do not have their own blood supply, and revascularization depends on the limited microcirculation system in the peripheral normal bone tissue of femoral head, which limits effectiveness of these treatments [23]. The vascularization of graft substitutes is still a huge problem in repair of ONFH. Many strategies were used to promote vascularization in bone tissue engineering, such as the application of growth factors [25,26], stem cells [27,28], bioactive materials [29], and the transplantation of vascular bundles [30–33]. Among these strategies, vascular bundle transplantation can not only provide additional blood supply but also promote the formation of new blood vessels, which makes it a potential method to improve blood supply for the necrotic femoral head. Therefore, we proposed a novel treatment strategy for ONFH through vascular bundle transplantation combined with porous titanium scaffold implantation [34].

ONFH model was established by cryo-insult method with liquid nitrogen as described in literatures. Histological examination showed most bone lacunae in trabecula of the normal femoral head were filled with deeply stained osteocyte nuclei (Fig. 2C). While the cryo-insult side was filled with a large number of empty osteocyte lacunae (Fig. 2D). This was consistent with previous studies, supporting reliability of this model [13,14].

After the necrotic bone was removed, traditional porous scaffold and experimental scaffold carrying vascular bundle were implanted into core decompression tunnel to mechanically support the subchondral bone. The two ends of vascular bundle in PTSV group were anastomosed with transverse branch of lateral femoral circumflex artery and its accompanying vein to form an arteriovenous loop for improving blood supply of implanted scaffold and femoral head. Compared with PTS group, more new blood vessels were formed in porous area of experimental scaffold (Fig. 6), indicating the implantation of vascular bundles brought more effective vascular reconstruction in necrotic area of femoral head. This was supported by previous studies of vascular bundle transplantation in different applications [31,32]. Micro-CT analysis showed significantly more bone ingrowth in PTSV group at three and six months after implantation (Fig. 5B), indicating that the introduction of new blood supply had brought better osseointegration effect. Histological analysis showed that newly formed bone tissue in traditional scaffold was much less and mostly confined to the surface of metal column, and the PTSV group had more bone ingrowth and higher porosity filling rate (Fig. 5A). Effective revascularization was thought to be the reason for better bone repair in PTSV group. Since improvement of blood supply had been well proven to enhance bone regeneration and repair ability in literatures [31,32,35]. However, we also found that there was almost no new bone tissue ingrowth in the window and internal U-shaped tunnel of the experimental scaffold. This was supported by previous studies, which believed that a diameter of 200–600 μm was suitable for blood vessels and bone tissue ingrowth [36–38], and it was very difficult for bone tissue to grow in areas with large holes like scaffold window and internal U-shaped tunnel area.

Due to the different mechanical environments between quadrupeds and humans, ONFH models usually could only simulate osteonecrosis without collapse [13]. This was also found in the present study that no animal showed obvious collapse of femoral head during the entire experimental period. Therefore, the repair of necrotic area was often

![Fig. 4](image-url) Micro-CT analysis of bone ingrowth in PTS and PTSV groups. *: P < 0.05.

![Fig. 5](image-url) A: Von-Gieson staining for histological analysis of bone ingrowth in different groups at 3 and 6 months postoperatively. B: Bone ingrowth of PTSV and PTS groups evaluated by histological analysis. The light red area represented bone tissue; the black area represented porous titanium scaffold. 3 M: 3 months postoperatively; 6 M: 6 months postoperatively; Yellow dotted line representing ROI. *: P < 0.05.
used to evaluate effect of various interventions [39].

As a preliminary study, it also had some limitations, including a small sample size, relatively short observation time. The reliability of this innovative technique requires more research evidence. The complications of this operation include the risk of affecting the blood flow of the limbs and damaging the saphenous nerve. If the great saphenous vein is used for clinical treatment, it may affect the source of the transplanted vessels, such as saphe-

5. Conclusion

This study proposed a novel device for treatment of ONFH, and preliminary proved its feasibility and effectiveness for the first time. It has the potential to provide new possibilities for rebuilding the blood supply of femoral head and repairing osteonecrosis. Further improvement of this device and investigating the effect of different vascular anastomosis methods will contribute to the further development of this novel treatment method.

Authorship statement

Bo Li: Conception and design of study, acquisition of data, analysis and/or interpretation of data, Drafting the manuscript, Approval of the version of the manuscript to be published. Lingjia Yu: acquisition of data, Approval of the version of the manuscript to be published. Yongxin Liang: acquisition of data, Approval of the version of the manuscript to be published. Guanping Li: analysis and/or interpretation of data, Approval of the version of the manuscript to be published. Yu Zhao: Conception and design of study, revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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