Effect of platelet-rich plasma scaffolding combined with osteochondral autograft transfer for full-thickness articular cartilage defects of the femoral condyle

Ming Li, Yiji Tu, Haojun Zhang, Yunfeng Zhang and Zhenglin Di

Department of Joint Surgery, Ningbo No. 6 Hospital, Ningbo, Zhejiang 315000, People's Republic of China

* Author to whom any correspondence should be addressed.
E-mail: lmjoint2019@163.com

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Abstract

We aimed to investigate the local application methods of platelet-rich plasma (PRP) and the effect and safety of PRP scaffolding combined with osteochondral autograft transfer (OAT) in the treatment of full-thickness articular cartilage defects of the femoral condyle. Patients with cartilage defects of the femoral condyle were treated with OAT combined with PRP scaffolding between July 2017 and December 2020. Preoperative magnetic resonance imaging (MRI) and computed tomography were utilized to assess the size, location, and severity of the osteochondral defects. X-ray and MRI images of the knee were obtained at the final follow-up to assess the osseointegration and integrity of the implanted articular cartilage. Osteoarthritic changes in the knee joint were evaluated using the Kellgren–Lawrence grading system. Clinical status was assessed using the visual analog scale (VAS), International Knee Documentation Committee (IKDC), and Lysholm scores before the treatment and at the final follow-up. Complications and patient satisfaction were recorded to assess the safety of this combination therapy. Twenty-one patients were recruited, with a mean follow-up duration of 18.23 ± 6.84 months. The mean lesion size was 2.3 ± 0.59 cm². The mean platelet concentration in PRP at baseline was 6.27 ± 0.63 times greater than that in the peripheral blood. The VAS, IKDC, and Lysholm scores had improved significantly at the final follow-up (P < 0.001). No serious complications such as joint infection, deep venous thrombosis, or hematoma were observed. Eighteen patients (85.72%) were satisfied with their knee function and quality of life at the final follow-up. Three patients (14.28%) complained of mild anterior knee pain, which was relieved by oral administration of nonsteroidal anti-inflammatory drugs. MRI examinations of all patients showed bony consolidation and the defect surface was covered with cartilage-like tissue. X-ray evaluations indicated that osteoarthritis in two knees (9.5%) had progressed from grade 1 to grade 2 at the final follow-up. The preliminary results showed that OAT combined with PRP may be a safe and effective technique for the treatment of full-thickness articular cartilage defects in the knee.

1. Introduction

Full-thickness articular defects have little capacity for self-healing. When such defects occur in the weight-bearing area of the knee joint, they invariably deteriorate and eventually progress to osteoarthritis. The treatment of such cartilage defects presents many challenges, especially in young and highly active individuals.

One of the most commonly used procedures to repair these defects involves transferring multiple cylindrical osteochondral autografts, a process called mosaicplasty by Hangody et al [1] and Bobic [2]. Previous studies have reported that osteochondral autograft transfer (OAT) achieved an effectiveness rate of 60%–80% for femoral condylar cartilage defects sized less than 2–4 cm² [3, 4]. Despite clinical improvement, a lack of peripheral integration of the cartilage...
is frequently observed [5]. Necrosis of the cartilage and nonunion of the graft with the surrounding tissues have also been observed [6]. Improving the efficacy remains a challenge for orthopedic surgeons.

Platelet-rich plasma (PRP) is a concentrated cocktail of autologous growth factors and has shown potential for use in cartilage repair. In preclinical studies, PRP has been used in gel form to fill cartilage defects and to slow the progression of arthritis in animal models with positive outcomes. Findings from recent clinical trials suggest that PRP may have the potential to fill cartilage defects and enhance cartilage repair, attenuate symptoms of osteoarthritis, and improve joint function with an acceptable safety profile [7].

Therefore, we propose that OAT combined with PRP may have a synergistic effect in the treatment of full-thickness cartilage defects, compensating for the deficiencies of mosaicplasty and improving the success rate. However, clinical research on PRP administration and its potential use as a therapeutic option for OAT is lacking. This study aimed to investigate the local application methods of PRP and clinical effect and safety of PRP scaffolding combined with OAT in the treatment of full-thickness articular cartilage defects of the femoral condyle.

2. Materials and methods

2.1. Patients

The present retrospective case series included patients treated with a combination of PRP and OAT. The PRP application procedure was approved by the Hospital Ethics Committee before the commencement of the study (No. 2015006). Enrolled patients were treated with OAT combined with PRP scaffolding from July 2016 to December 2020. All patients with femoral condylar cartilage defects during the study period were screened for inclusion. The inclusion criteria were as follows: (a) patients aged between 18 and 45 years, (b) symptoms or signs of knee cartilage defects, and (c) magnetic resonance imaging (MRI) or arthroscopic findings of full-thickness cartilage defects. The exclusion criteria were: (a) patients with pyogenic infection or severe osteoarthritis, (b) patients with a large or extensive cartilage defect (size >3.5 cm²) during the surgery, (c) abnormal knee alignment requiring peri-knee osteotomy, (d) previous surgical treatments of the ipsilateral knee, (e) pregnant or lactating women, (f) rheumatoid arthritis, (g) gout, (h) blood diseases, (i) severe cardiovascular diseases, (j) infections, (k) immunodepression, (l) patients receiving anticoagulant therapy, and (m) patients with hemoglobin level <11 g dl⁻¹ and platelet count <150 000 mm⁻³. Patients who did not complete 12 months of follow-up were also excluded from the study.

2.2. Preparation of platelet-rich plasma

For each preparation, 50 ml of blood was collected from the median cubital vein using a 50-gauge needle, ensuring that the ratio of blood to anticoagulant was 9:1. PRP was prepared using a standard collection program during the surgery as described previously [8]. The collected blood was transferred to a separation tube (Weigao New Polymer Materials Co., Ltd) and centrifuged twice: once to separate the erythrocytes and subsequently to concentrate the platelets (378 × g for 10 min each). Altogether, 5 ml of PRP was obtained. From this, 4.5 ml was immediately transferred to a sterile syringe and the remaining 0.5 ml was sent to the laboratory for platelet concentration analysis. PRP (2 ml) was mixed with decalcified bone matrix (DBM) (Wright, USA) powder to make a PRP-DBM compound. The remaining 2.5 ml of PRP was used for immersion and intra-articular injection. All procedures were performed within 25 min in the same operating room.

2.3. Surgical procedures and application of platelet-rich plasma

All surgical procedures were performed under general anesthesia by the same surgeon (ML), with patients in the supine position. All patients underwent careful routine arthroscopic inspection and evaluation of the chondral or osteochondral defects. The synovial tissue, menisci, ligaments, and location and size of the defect were carefully inspected (figure 1(a)) to identify the indications for OAT. The curve and cartilage thickness of the graft donor area were also evaluated. The femoral trochlea has a convex surface and low pressure, which makes it a suitable donor site comparable to the weight-bearing region of the condyles (figures 1(b) and (c)).

Soft tissue scars, sclerotic bone, and other abnormal tissues at the recipient site were cleaned to receive the donor plugs. A mini-open approach or accessory arthroscopic portals were created to allow orientation of the instruments (Smith-Nephew bone cartilage transplantation equipment) perpendicular to the articular surfaces at the donor and recipient sites. The plugs were immersed in PRP for at least 3 min (figure 1(d)). The PRP-DBM (figure 1(e)) compound was placed inside the defect before fixation (figure 1(f)). The plugs were introduced with gentle tapping and care was taken to place the plugs either flush with the surrounding tissues or 1 mm below the surrounding tissues (figure 1(g)). The space between the osteochondral plugs was filled with the PRP-DBM compound. The donor sites were left empty or filled with loose bone or DBM. In addition, the remaining PRP was injected into the joint following tight closure of the capsule (figure 1(h)).

One day after the surgery, the patients were instructed to perform straight leg exercises to prevent quadriceps atrophy. Continuous passive motion...
was utilized for 2–4 weeks. After the initial 6 weeks, the patients maintained touch-down weight bearing. Return to athletic activities was delayed for 6 months.

2.4. Clinical evaluation
Clinical assessment included a detailed history, physical examination, evaluation of pain and its severity, and association of pain with other symptoms such as locking, swelling, muscle atrophy, and joint space tenderness. Outcome assessments were performed by a clinician blinded to the treatment. Functional assessment included determination of the visual analog scale (VAS) and the International Knee Documentation Committee (IKDC) and Lysholm scores before the treatment and at the final follow-up. Complications and patient satisfaction were recorded to assess the safety of this combination therapy.

Preoperative MRI and computed tomography (CT) were utilized to assess the size, location, and severity of the osteochondral defects. Knee x-ray and MRI were obtained at the final follow-up to assess the osseointegration and integrity of the implanted articular cartilage. The donor site was also evaluated for congruence and osteochondral thickness. All images were interpreted by a single radiologist with extensive experience in the interpretation of x-ray, MRI, and CT images. The radiologist was blinded to the treatment and was not involved in clinical evaluation. The cartilage defects were graded according to the International Association of Cartilage Repair Association scale. Osteoarthritic changes in the knee joint were evaluated using the Kellgren–Lawrence grading system.

2.5. Statistical analysis
The data are expressed as mean ± standard deviation unless indicated otherwise. A paired t-test was performed to assess the differences between the pre-treatment clinical scores and those at the final follow-up. Statistical analyses were performed using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, United States) and \( P \)-values <0.05 were considered statistically significant.

3. Results
3.1. Baseline data
Altogether, 21 patients (21 knees) aged 18–43 years (32.0 ± 6.34 years) met the inclusion criteria and completed more than 12 months of follow-up. Fourteen (66.7%) patients had suffered some trauma, while seven (33.3%) patients had no obvious history of trauma. The main symptoms were knee pain and limited mobility with locking in six patients and a ringing sound in five patients. The mean follow-up duration was 18.23 ± 6.84 months. The most common defect location was the medial condyle (13 cases), followed by the lateral condyle (8 cases). Meniscal suturing was performed in seven cases due to bucket handle tears and partial meniscectomy. The mean lesion size was 2.3 ± 0.59 cm². The mean defect depth was 4.45 ± 0.71 mm. The platelet count of PRP was 817.31 ± 168.22 \( \times 10^9 \) l\(^{-1}\), which was 6.27 ± 0.63 times greater than that in the peripheral blood (table 1).

3.2. Clinical evaluation
Preliminary analysis of the PRP and control groups demonstrated a statistically significant improvement.
in clinical scores. The VAS scores decreased significantly from 7.0 ± 1.45 at baseline to 1.73 ± 1.04 at the final follow-up (P = 0.000). Similar results were observed for the IKDC and Lysholm scores. The IKDC score increased from 37.63 ± 7.56 at baseline to 69.68 ± 5.75 at the final follow-up (P = 0.000). The Lysholm score increased from 55.89 ± 6.05 at baseline to 74.89 ± 7.23 at the final follow-up (P = 0.000) (table 2).

No complications, such as infection, deep venous thrombosis, and hematoma or other major adverse events, were observed. Eighteen patients (85.72%) were satisfied with their knee function and quality of life at the final follow-up. Three patients (14.28%) complained of mild anterior knee pain, which was relieved by oral administration of nonsteroidal anti-inflammatory drugs. MRI examinations of all patients revealed bony consolidation and the surface of the defect was covered with cartilage-like tissue (figures 2(c) and (d)). X-ray evaluations indicated that knee osteoarthritis had progressed from grade 1 to grade 2 in two knees (9.5%) at the final follow-up (figures 3 and 4).

4. Discussion

The OAT technique is a single-stage procedure that involves placement of osteochondral plugs in a cartilage defect in the weight-bearing region of the knee. Hangody et al [1] reported satisfactory results of OAT in the treatment of 152 full-thickness knee cartilage defects. Gomoll et al [9] reviewed surgical treatments of knee cartilage defects and found that OAT exhibited good to excellent results in 60%–80% of patients. They suggested using the technique in defects sized below 2–4 cm², since healthy graft tissue can only be obtained from a limited area of the same joint [9]. At an average follow-up of 18.23 months after the surgery, 85.72% of the patients in the present study were satisfied with their knee function and quality of life at the final follow-up. MRI examinations of all patients showed bony consolidation and the defect surface was covered with cartilage-like tissue. This outcome was better than that reported by Gomoll et al, which might be due to the combined application of PRP and OAT. The relatively small lesion size (2.3 ± 0.59 cm²) in the present study might be another reason for the better outcome. Gomoll et al [9] reported that the outcomes in patients aged over 30 years were not as good as those in younger patients. However, two other studies suggested that patients aged below 45 years exhibited better outcomes following OAT [4, 10]. Patients in the present study were aged 18–43 years and we believe that young patients have a high chance of successful outcomes following the surgery. This technique has several advantages, such as newly formed mature hyaline cartilage, primary bone healing, and quicker recovery. It has been shown that although osseointegration between the recipient and donor bone can occur at 4 weeks after the transplantation [1], gaps between the donor cartilage and recipient site persist. Evaluation at 8 weeks revealed that the intervening connective tissue was fibrocartilage [1, 2]. Lane et al [4] reported that a lack of peripheral integration of the cartilage is frequently observed. Patil et al [6] noted that necrosis of the cartilage and nonunion of the graft with the surrounding tissues have also been observed. These possible reasons for failure have motivated us to explore biological approaches to improve clinical outcomes.

In recent years, several studies have confirmed that PRP can promote the proliferation of osteoblasts and chondrocytes, promote the synthesis of extracellular matrix, and repair the damaged bone and articular cartilage [11]. In addition, PRP can reduce intra-articular synovial hyperplasia and adjust the concentration of the surrounding active proteins [12]. Intra-articular use of PRP may also have an effect on fibroblast-like synoviocytes, which can produce hyaluronic acid (HA) and cytokines found in the synovial fluid [13]. Thus, the effect of PRP on synoviocytes may indirectly influence the repair of cartilage injury. Inactive PRP is in the liquid form and can be used for injection. PRP in the gel form contains large amounts of platelets and fibrin. PRP gels not only release growth factors slowly but also provide a three-dimensional scaffold vector for cell growth [14, 15].

Only a few clinical reports on treatment of cartilage defects using PRP have been published and all of these were case reports. The authors attributed the success of the treatment to the addition of PRP, which
augmented the reattachment of the cartilage fragment [16]. Haleem et al [17] seeded autologous expanded bone marrow-derived mesenchymal stem cells into the PRP gel to fill full-thickness cartilage defects in femoral condyles. Five patients aged 21–37 years were included, with defects ranging from 3–12 cm² in size. All patients exhibited improvement in the symptoms over a follow-up period of 12 months. Dhollander et al [18] reported treatment of five patients with patellar cartilage defects ranging from 1–3 cm² in size. The patients were treated with microfracture and filing the defects with leukocyte- and PRP gel. The defects were sealed with collagen I/III membranes. The symptoms and knee function of all five patients improved markedly after the surgery [18].

Reportedly, intra-articular injection of PRP may be an attractive approach for the treatment of knee osteoarthritis. Lisi et al [7] performed a phase-2 randomized controlled trial wherein 50 patients received three intra-articular injections of activated PRP or HA at 4 week intervals. Activated PRP reduced articular damage within 6 months after the treatment, which was confirmed by MRI examinations. Kon et al [19] compared the clinical benefits of PRP with those of low molecular weight and high molecular weight HA. The results showed improved performance in the PRP group at the 6 month follow-up examination among patients aged <50 years. Although the results were encouraging, the study had a short follow-up duration and a small sample size. Moreover, it had the same limitations as those associated with the aforementioned study by Lisi et al [7]. Two systematic reviews concluded that intra-articular injections of PRP provided better symptomatic relief in patients having early degenerative changes in the knee and should be considered in patients with knee osteoarthritis [20, 21]. However, studies have also reported certain negative aspects of PRP injection therapy. In 2016, Filardo et al [22] performed a randomized blinded controlled trial including 192
patients with knee osteoarthritis (96 treated with HA and 96 with PRP), with 12 months of follow-up. They concluded that PRP injections were not more beneficial than treatment with HA. The authors also highlighted another concern. PRP preparation involved harvesting 150 ml of peripheral blood followed by two centrifugation steps, which provided 20 ml of PRP. After the first injection of 4–5 ml, the remaining PRP was frozen for 2 weeks and then thawed for the second and third injections. It was suggested that storing PRP at $-20^\circ C$ and then thawing for subsequent use may decrease the levels of growth factors significantly \[23\], thus altering the clinical effects of PRP.

In the present study, after a mean duration of 18.23 months, only two of the 21 patients showed progression of osteoarthritis from grade 1 to grade 2, while the remaining patients exhibited no progression in the grade of osteoarthritis. PRP might have played a role in this result. The most important finding of the study was that OAT combined with PRP was a safe and effective technique for the treatment of full-thickness articular cartilage defects of the knee. Using a New Zealand rabbit model, Altan et al \[24\] showed that adjunctive use of PRP produced a better healing response and resulted in superior histological scores after 3 weeks when compared with mosaicplasty alone. However, no significant difference was observed in the transition zone between the groups at 6 weeks after the experiment. The authors proposed that inadequate amount of PRP (single administration with fourfold higher platelet concentration) was the main reason behind this finding \[24\]. PRP used in the present study had a 6.27-fold greater platelet concentration than that in the peripheral blood. However, it was administered only once. Milano et al \[25\] suggested repeated injections to obtain long-term effects and better histological scores.

To maximize the utility of PRP, the present study utilized the following three improved methods of PRP administration. (a) Immersing the plugs in PRP might have allowed enough amount of PRP to penetrate into the cancellous bone space. (b) PRP was mixed with DBM powder to make a PRP-DBM compound, which was packed into the recipient area and into the plug gaps to stabilize and fix the plugs. (c) PRP was injected into the joint following tight closure of the capsule. For slower activation of PRP and consequent prolonged growth factor activity, calcium chloride was not used before the injection. Instead, pure PRP was directly injected to enable even distribution within the joint. To avoid freezing, PRP was produced from fresh peripheral blood before each injection, which ensured the freshness of PRP and reduced the possibility of exogenous contamination.

5. Conclusion

The present preliminary follow-up study showed that OAT combined with PRP achieved satisfactory results in the treatment of knee cartilage defects. However, the present study has several limitations such
as small sample size and the lack of a control group. Patients were followed up for a mean duration of 18.23 months, which was not adequate to study the long-term efficacy and effects of OAT on knee degeneration. In the present study, most of the patients were satisfied with their knee function and quality of life at the latest follow-up. However, three patients complained of anterior knee pain and discomfort. This finding might be due to donor site complications, although we did not have direct evidence of patellofemoral arthritis.

Data availability statement

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

All data that support the findings of this study are included within the article (and any supplementary files).

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Ethics approval

Written informed consent for publication of this paper was obtained from the Ethics committee of the Ningbo No.6 hospital (No. 2015006).

Study declaration

The study was done in accordance with local statutory requirements and the Declaration of Helsinki.

Consent to participate

All patients gave written informed consent before participation in this study.

Consent to publish

The work described was original research that has not been published previously, and not under consideration for publication elsewhere. The manuscript was approved by all authors for publication.

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Author contributions

M L and Y T designed the study, performed the experiments and drafted the manuscript. H Z Y Z and Z D performed the experiments, analyzed the data, and helped to draft the manuscript. All authors read and approved the final manuscript.

ORCID iD

Ming Li @ https://orcid.org/0000-0001-9223-1508

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