Biomedical Research and Therapy, 2014 (1):02-08
ISSN 2198-4093
www.bmrat.org

DOI 10.7603/s40730-014-0002-9

ORIGINAL RESEARCH

Symptomatic knee osteoarthritis treatment using autologous adipose derived stem cells and platelet-rich plasma: a clinical study

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Received: 15 December 2013 / **Accepted**: 02 February 2014 / **Published online**: 7 February 2014

Abstract—Osteoarthritis is one of the most common diseases, and it affects 12% of the population around the world. Although the disease is chronic, it significantly reduces the patient's quality of life. At present, stem cell therapy is considered to be an efficient approach for treating this condition. Mesenchymal stem cells (MSCs) show the most potential for stem cell therapy of osteoarthritis. In fact, MSCs can differentiate into certain mesodermal tissues such as cartilage and bone. Therefore, in the present study, we applied adipose tissue-derived MSCs to osteoarthritis treatment. This study aimed to evaluate the clinical efficiency of autologous adipose tissue-derived MSC transplantation in patients with confirmed osteoarthritis at grade II and III. Adipose tissue was isolated from the belly, and used for extraction of the stromal vascular fraction (SVF). The SVF was mixed with activated platelet-rich plasma before injection. The clinical efficiencies were evaluated by the pain score (VAS), Lysholm score, and MRI findings. We performed the procedure in 21 cases from 2012 to 2013. All 21 patients showed improved joint function after 8.5 months. The pain score decreased from 7.6±0.5 before injection to 3.5±0.7 at 3 months and 1.5±0.5 at 6 months after injection. The Lysholm score increased from 61±11 before injection to 82±8.1 after injection. Significant improvements were noted in MRI findings, with increased thickness of the cartilage layer. Moreover, there were no side-effects or complications related to microorganism infection, graft rejection, or tumorigenesis. These results provide a new opportunity for osteoarthritis treatment. Level of evidence: IV.

Keywords—Osteoarthritis, Adipose tissue-derived stem cell, Stromal vascular fraction, Platelet-rich plasma.

INTRODUCTION

Cartilage injury is a common clinical condition, especially in people aged over 40 years. Such injuries can lead to osteoarthritis if they are not suitably treated. Osteoarthritis is a chronic degenerative progression that results in cartilage degeneration, osteophytes, reorganization of side-bone, and loss of joint function (Wieland et al., 2005). At the present time, cartilage injuries are treated with drugs (Dougados, 2001; Eyigor et al., 2006) or injection with hyaluronic acid (Chen et al., 2011; Karatosun et al., 2008; Spakova et al., 2012) to reduce symptoms and pain, and control inflammation. However, these therapies have limited efficiency and fail to prevent disease progression (Schroeppel et al., 2011).

Cultured chondrocyte transplantation has also been used to treat cartilage injury since 1994. Autologous chondrocytes are isolated and expanded before injection into the joint. Cultured chondrocyte transplantation has provided some good outcomes (Frisbie et al., 2008; Kreuz et al., 2013; Lee et al., 2003). However, this method also has some limitations, especially the lack of cultured chondrocyte sources, as almost all cultured chondrocytes die after long-term culture because of maturation.

A recent study showed the presence of stem cells in adipose tissue, and termed these cells adipose-derived stem cells

(ADSCs). These cells are considered to be mesenchymal stem cells (MSCs) that exhibit some particular properties. They are able to adhere to the flask surface with a fibroblast-like shape, and successfully differentiate into osteoblasts, chondrocytes, and adipocytes (Zuk et al., 2001). They also express particular markers of MSCs, such as CD44, CD73, CD90, and CD105, but are negative for CD14, CD34, and CD45 (Gaiba et al., 2012; Khan et al., 2012; Zhu et al., 2012; Zimmerlin et al., 2013). This profile is similar to the profile of MSCs described by Dominici and colleagues (Dominici et al., 2006). Compared with MSCs from bone marrow and umbilical cord blood, ADSCs have many advantages (Christodoulou et al., 2013). In particular, ADSCs represent a suitable autologous cell source. To date, ADSCs have become excellent candidates for research and clinical applications. Many studies have shown that ADSC transplantation efficiently improved almost all symptoms of certain diseases, such as liver fibrosis (Harn et al., 2012), nerve defects (Gu et al., 2012; Liu et al., 2011; Santiago et al., 2009), ischemia (Mazo et al., 2012; Rigol et al., 2010), skeletal muscle injury (Pecanha et al., 2012), passive chronic immune thrombocytopenia (Xiao et al., 2012), and myocardial infarction (Yang et al., 2012) in animals, and systemic sclerosis in humans (Riordan et al., 2009; Scuderi et al., 2013).

Given the huge potential of ADSCs, many studies have been conducted over the last few years, including preclinical trials and clinical trials carried out to treat cartilage injury and osteoarthritis. Some of the animal models used were dogs (Black et al., 2008; Black et al., 2007; Guercio et al., 2012), rabbits (Toghraie et al., 2011), horses (Frisbie et al., 2009), rats (Lee and Im, 2012), mice (ter Huurne et al., 2012; Van Pham et al., 2013b), and goats (Murphy et al., 2003).

In another study, however, ADSCs were considered to inhibit cartilage regeneration. This conclusion was drawn from experiments of ADSC transplantation in rats. The study showed that ADSCs highly expressed and secreted VEGF-A into the culture supernatant. The supernatant was found to inhibit chondrocyte proliferation, reduce Sox9, alcan, and collagen II mRNA levels, reduce proteoglycan synthesis, and increase apoptosis. Histological examination revealed that defects with ADSCs had no tissue ingrowth from the edges of the defect (Lee et al., 2012).

In previously published studies, we evaluated the in vitro and animal model (mice) effects of platelet-rich plasma (PRP) on ADSC differentiation into chondrocytes. In vitro, we showed that PRP treatment of ADSCs promoted their differentiation and proliferation into chondrogenic cells (Van Pham et al., 2013a). These cells strongly expressed collagen II, Sox9, and aggrecan. As a result, PRP-pretreated ADSCs improved healing of injured articular cartilage in a mouse model compared with untreated ADSCs. In another study, we investigated the effects of PRP on non-expanded stromal vascular fraction (SVF) transplantation in a cartilage injury mouse model, and observed great regeneration of cartilage (Van Pham et al., 2013b). Moreover, there were no non-beneficial effects from ADSC or SVF transplantation recorded in the animal models (Van Pham et al., 2013a).

Based on these results, we performed this clinical trial with the aim of evaluating the efficiency and side-effects of non-expanded SVF transplantation in combination with PRP in osteoarthritis grade II and III.

MATERIALS – METHODS

Inclusion criteria

All patients enrolled in this study were required to sign the consent form. All procedures used in the study were approved by the Ethical Committee of the University Medical Center, Ho Chi Minh University of Medicine and Pharmacy (Ho Chi Minh City, Vietnam).

Regarding inclusion criteria, all patients were aged above 18 years, had osteoarthritis from cartilage injury at grade II to III, had failed in drug treatment as well as autologous cartilage transplantation, had a Lysholm score lower than 65, were committed with a surgical condition, and were HIV-negative.

A total of 21 patients were enrolled in the study. The study was designed with the endpoint classification of safety and efficacy, the intervention model was single group assignment without a control, the masking was open label, and the primary purpose was treatment.

Isolation of SVF from adipose tissue

The SVF was isolated from the abdominal adipose tissue of each patient. For this, approximately 50–100 ml of lipoaspirate was collected from each patient into two 50-ml sterile syringes. All procedures and manipulations were approved the Hospital Ethical Committee (Ho Chi Minh City Medicine and Pharmacy University Hospital, Ho Chi Minh City, Vietnam). The syringes were stored in a sterile box at 2–8°C and immediately transferred to the laboratory. The SVF was isolated using an ADSC Extraction Kit (GeneWorld, Ho Chi Minh City, Vietnam) according to the manufacturer's instructions. This kit was approved by the Vietnam Ministry of Health as a medical device. Briefly, 50–100 ml of lipoaspirate was placed in a sterile disposable 250-ml conical centrifuge tube (Corning, Tewksbury, MA) and washed twice with sterile PBS by centrifugation at 400×*g* for 5 min at room temperature. Next, the adipose tissue was digested using SuperExtract Solution containing collagenase at 37°C for 30 min with agitation at 5-min intervals. The suspension was centrifuged at 800×*g* for 10 min, and the SVF was obtained as the pellet. The pellet was washed twice with PBS to remove any residual enzyme, and resuspended in PBS for determination of

the cell quantity and viability using an automatic cell counter (NucleoCounter; Chemometec, Denmark).

Activated PRP preparation

Activated PRP was derived from the peripheral blood of the same patient as the adipose tissue using a New-PRP Pro Kit (GeneWorld) according to the manufacturer's guidelines. Briefly, 20 ml of peripheral blood was collected into vacuum tubes and centrifuged at 800×*g* for 10 min. The plasma fraction was collected and centrifuged at 1000×*g* for 5 min to obtain a platelet pellet. Most of the plasma was then removed, leaving 3 ml of plasma for resuspension of the platelets. This preparation was inactivated PRP. Finally, PRP was activated using activating tubes containing 100 µl of 20% $CaCl_2$.

Preparation of product for transplantation

The product for injection was a mixture of the obtained SVF and activated PRP. Activated PRP was used to dilute the SVF to achieve a suitable dose for injection.

Injection of product and monitoring

All patients were examined and evaluated according to the inclusion criteria at 2 weeks before the transplantation. All patients were re-evaluated at 1, 3, and 6 months post-transplantation. The primary outcome measurements included the Lysholm score, change from baseline in quality of life score, and number of adverse events reported (after 1, 3, and 6 months). The secondary outcome measurements were changes from baseline in X-rays of the affected joint (MRI score) (after 6 months).

All patients were examined after collection of aspirated adipose tissue and peripheral blood to obtain the SVF and activated PRP. The patients waited in the surgery room for 2 h before receiving the injected mixture of SVF and PRP without joint surgery.

RESULTS

This study started in early 2012 and finished in early 2013. All patients examined had osteoarthritis at grade II to III. The results showed that were significant improvements in joint function after 8.5 months. The pain score (VAS Walking Index) changed significantly and gradually decreased from 7.6±0.5 before injection to 3.5±0.7 after 3 months and 1.5±0.5 after 6 months. The Lysholm score also improved significantly and gradually increased from 61±11 before injection to 71±13 after 3 months and 82±8.1 after 6 months.

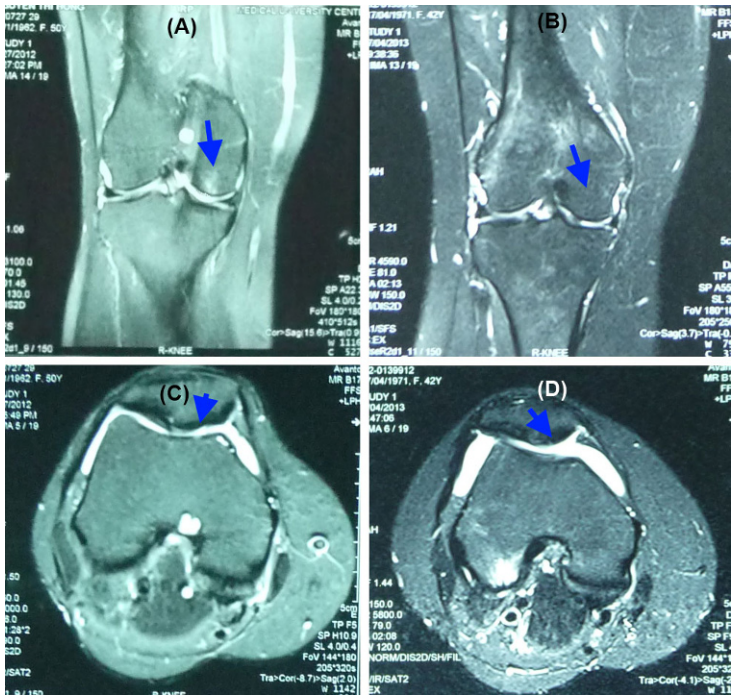

Figure 1. MRI analysis of a joint before and after SVF and PRP injection. At 6 months after injection, MRI signals showed that there were some improvements in the injured cartilage and regeneration of the injured cartilage sites (B) compared with the pretreatment condition (A). The cartilage layer was also thicker (D) compared with the pretreatment condition (C).

Regarding the histology, MRI analysis showed that the cartilage layers were partly regenerated at the injured sites. The MRI pictures showed that the cartilage layer was also thicker after 6 months of treatment.

Overall, 100% of patients were pleased with the treatment results. They felt that their pain levels gradually reduced, especially after 3 months. There were 15 patients (71.24%) who could go up and down stairs after 3 months. Currently, 100% of patients can move normally and carry out normal living activities. More importantly, 100% of patients had no side-effects or complications related to the procedure, such as microorganism infection or tumor formation at the joint.

Discussion

Knee osteoarthritis is a common chronic orthopedic disease that significantly reduces the patient's quality of life. In recent years, stem cell application to osteoarthritis has rapidly developed, with promising results in preclinical and clinical trials. This clinical study showed that SVF and PRP injection brought about some good outcomes for patients with osteoarthritis.

One of the clear results regarding the effects of the SVF and PRP injection was that the patients could feel pain reduction. In fact, the VAS score was significantly decreased after 6 months (from 7.6±0.5 to 1.5±0.5). Pain reduction is related to the role of PRP. At the present time, PRP is widely used for certain clinical conditions, especially in the management of pain and inflammation. PRP was reported to inhibit the NFκB cascade, by preventing the induction of NFκB from IκB*α*, thereby trapping NFκB in the cytoplasm and preventing the induction of NFκB target genes (van Buul et al., 2011). In a previous study, it was shown that NFκB was activated by IL-1β in chondrocytes obtained from osteoarthritis patients. Once NFκB is activated, almost all gene-related anabolic pathways, such as type II collagen and aggrecan synthesis, are blocked. However, PRP treatment can rescue these pathways (van Buul et al., 2011; Wu et al., 2011).

The anti-inflammatory and pain reduction effects are also related to growth factor components in PRP. PRP contains a pool of cytokines, including HGF, PDGF, IGF, TGF-β, EGF, and FGF (Amable et al., 2013; Banfi, 2012; Hamilton et al., 2013). HGF was proven to act as an enhancer of NFκB inhibitor (Bendinelli et al., 2010), decrease the production of the cytokine IL-6, and increase the anti-inflammatory cytokine IL-10 (Coudriet et al., 2010). TGF-β1 abolishes CXCR4 expression in monocytes (Bendinelli et al., 2010; Coudriet et al., 2010). IGF-1 and PDGF also inhibit activation of NFκB (Montaseri et al., 2011).

The anti-inflammatory and pain reduction effects are also partly contributed by soluble factors secreted from the SVF or ADSCs. ADSCs secrete many important soluble factors, such as HGF, VEGF, NGF, EGF, FGF, and TGF-β (Kilroy et al., 2007; Salgado et al., 2010; Van Pham et al., 2013a). Unlike PRP, growth factors from ADSCs are continuously produced after injection of these cells into the joint.

The second effect of SVF and PRP injection was stimulation of cartilage growth at the injected sites. The results showed that the cartilage layer gradually became thicker at 3 and 6 months after injection, and that some injured cartilage sites in particular were regenerated. These findings arise from the combined effects of ADSCs and PRP. In some of our previous studies in mouse models, we recorded that SVF and PRP as well as ADSC and PRP stimulated neocartilage formation (Van Pham et al., 2013a; Van Pham et al., 2013b). As ADSCs highly express VEGF-A, which inhibits the growth of cartilage, transplantation of ADSCs alone can inhibit cartilage growth (Lee et al., 2012). In this research and a previous study in a mouse model (Van Pham et al., 2013a), we used ADSCs in combination with activated PRP to inhibit VEGF production, thereby improving ADSC differentiation into chondrocytes.

The existence of grafted ADSCs at injected sites as well as the participation of ADSCs in neocartilage formation were not verified in this study. However, in another study (data not shown), we labeled human ADSCs with GFP and injected them into the joints of NOD/SCID model mice. At 30 days after transplantation, GFP-labeled cells at the knee cartilage were collected and evaluated for the expression of certain genes related to chondrocytes, such as collagen type II, aggrecan, and Sox9. The results showed that GFP-labeled cells strongly expressed these genes. These findings showed that ADSCs in the knee joint microenvironment were induced to differentiate into chondrocytes.

The beneficial effects of ADSC transplantation have also been recorded in clinical trials in certain countries. In a recent study, Jo et al. (2014) performed a clinical study involving treatment of knee osteoarthritis by injection of ADSCs in 18 patients. After 6 months, patients injected with 1×10^8 cells had significantly improved WOMAC score and size of cartilage defect, with no adverse events (Jo et al., 2014).

In a study involving fewer patients, Pak (2011) reported that almost all patients showed significant improvements in all clinical outcomes at the final follow-up examination. All clinical results were significantly improved at the 2-year follow-up compared with the 12-month follow-up (Pak, 2011).

Conclusion

To summarize, autologous SVF injection in combination with PRP is a safe and efficient method for treating osteoarthritis of grade II and III. The efficiency of transplantation clearly improved after 6 months. Overall, 100% of patients

were pleased with this method. Pain was strongly reduced after 3 months, the cartilage layers were thicker after 6 months, and the quality of life was significantly improved. Although further studies with control subjects and more patients need to be performed to confirm the above results, this study suggests that our treatment is a promising minimally invasive therapy for osteoarthritis patients.

ACKNOWLEDGMENT

This work was funded by grants from GeneWorld Ltd. SHTP, HCM, VN.

Abbreviations

MSCs: Mesenchymal stem cells; SVF: Stromal vascular fraction; ADSC: Adipose derived stem cell; VEGF: Vascular endothelial growth factor; PRP: Platelet rich plasma; PBS: Phosphate buffered saline; TGF-β: transforming growth factor-beta; EGF: epidermal growth factor; bFGF: basic fibroblast growth factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors read and approved the final manuscript. KHTB, TDD, NTN, TDN, VTL, VTM carried out the clinical surgery, included adipose aspirate, SVF and PRP injection. NLCP, DML isolated SVF and PRP preparation. NKP participated in designing the study. PVP prepared the manuscript in cooperation with all other authors.

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Cite this article as:

Bui, K., Duong, T., Nguyen, N., Nguyen, T., Le, V., Mai, V., Phan, N., Le, D., Phan, N., & Pham, P. (2014). Symptomatic knee osteoarthritis treatment using autologous adipose derived stem cells and platelet-rich plasma: a clinical study. *Biomedical Research And Therapy*, *1*(1):2-8.