Pre-SVF arthroscopy: A case report of new concept of meniscus and cartilage regeneration using arthroscopy followed by intra-articular injection of adipose-derived stromal vascular fraction

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Abstract

Background: A series of clinical case reports demonstrating the intra-articular injection of autologous adipose-derived stem cells (The Stromal Vascular Fraction - SVF) combined with platelet rich plasma (PRP), hyaluronic acid, and calcium chloride after arthroscopy procedure (Pre-SVF Arthroscopy) has a therapeutic potential to regenerate cartilage in knee osteoarthritis for elderly patient and athletes with meniscus tears as well as preventing re-tears occurrence.

Case presentation: A study of three patients underwent arthroscopy procedure for unilateral knee followed by stem cells intra-articular injection that were obtained from abdominal adipose tissue by digesting lipoaspirate tissue with collagenase. The adipose-derived stem cells (Stromal Vascular Fraction - SVF) were injected into the patients knee along with hyaluronic acid, platelet rich plasma and calcium chloride after the arthroscopy procedure. All patients had an injury of medial or/and lateral meniscus, osteoarthritis, history of pain and limitation of motion. Pre-treatment and post-treatment MRI scans, modified functional rate index and pain score data were then analyzed.

Conclusion: Some patients may suffer from meniscus injury with symptoms such as locked knee, which may not benefit significantly with SVF intra-articular injection solely. The Pre-SVF arthroscopy procedure has shown to solve the mechanical related symptoms of the knee movement and to regenerate damage tissues, without complication or risk of early onset osteoarthritis. This clinical study conducted three patients underwent Pre-SVF arthroscopy which gain significant clinical improvement and MRI evidence of meniscus and articular cartilage regeneration.

Keywords: Adipose derived stem cell, meniscus tear, knee osteoarthritis, Pre-SVF arthroscopy, autologous mesenchymal stem cell, case report

Background

The menisci are two semilunar, fibro-cartilaginous discs located between the medial and lateral articular surfaces of the femur and tibia which have a key function of (i) transfer of weight, (ii) absorb shocks, and (iii) cartilage protection [1]. The meniscus injury can be diagnosed with clinical examination and confirmed by MRI scans [2]. The pain caused by meniscus injury is initially treated conservatively [3,4]. If the conservative treatment fails, a meniscectomy is considered. However, the meniscectomy treatment -or even partial one- is associated

with early onset of osteoarthritis of the knee [5-8]. Further, The New England Journal of Medicine published a series of controlled clinical trials showing limited effects of arthroscopic surgery for the treatment of OA [9-12]. Common conservative treatment including physical therapy, viscosupplementation [13], glucosamine and/or chondroitin sulfate [14], and acupuncture [15] have demonstrated modest to no clinical benefit when compared with placebo. The objective of these treatments tend to decrease pain, maintain or improve joint function, and minimized disability, without regenerating the

joint tissue. However, the regeneration of articular cartilage and meniscus via intra-articular introduction of mesenchymal stem cells (MSCs) has been showing promising results which have a great potential as a future therapeutic agent in the field of regenerative medicine. We have seen much *in vitro* [16-18], *in vivo* [19-30], and clinical [31-43] experimentation on MSCs.

MSCs are multipotent cells that can be extracted from bone marrow and adipose tissue of abdomen, thigh and hips [44,45]. MSCs are capable to differentiate into bone, cartilage and muscle, and represent promising therapy in regenerative medicine [31-33]. Reports of successful regeneration of bone and cartilage in humans have been demonstrated using various MSCs [32-43], particularly adipose-derived stem cells (ADSCs) [35-40]. However, there are a lack of studies on regenerative medicine via intra-articular injected MSCs of middle-age patients or athletes who has absolute indication of knee arthroscopy which been demonstrated in some studies [46,47]. We have seen a report study with a promising result of rotator cuff repair followed by BM-MSCs which improve healing and prevent re-tear [48]. However, there are no relevant studies on knee or hip cases (as we aware of).

Case presentation

On April 21, 2009, Guideline for transplantation and treatment with tissue engineering (TE) techniques was issued by the Ministry of Health of P.R. China [49]. Here, we present case study report on a successful clinical results using intra-articular injected autologous ASCs along with platelet-rich plasma (PRP), hyaluronic acid and CaCl₂ following the arthroscopy procedure.

The inclusion criteria, exclusion criteria, and endpoints of the outcome are listed in **Tables 1-3** [40].

Patients history

Patient 1

The patient is a 47-year-old male athletes presented with left knee pain and limitation of movement due to past injury, he

Table 1. Including criteria.

Description
1. MRI evidence of meniscus tear.
2. Absolute indication for arthroscopy (i.e., Locked knee, mechanical LOM due to osteophytes.
3. Willing to proceed with arthroscopic partial meniscectomy.
4. Failure of conservative treatment.
5. Continuous pain.

Table 2. Exclusion criteria.

Description
1. Active inflammatory or connective tissue disease (i.e. lupus, RA).
2. Active neurologic disorder (i.e. peripheral neuropathy, multiple sclerosis).
3. Severe cardiac disease.

Table 3. Outcome data collection.

Description
Pre and post treatment visual analog scale (VAS).
Pre and post treatment functional rating index (FRI).
Pre and post treatment range of motion.
Pre and post treatment MRI.

had a daily pain score 4/10 increased to 7/10 with walking. On physical examination, there was medial joint tenderness and positive patellar grind test. Apley's and McMurray tests were positive, and no joint swelling, range of motion as in **Table 4**. Pre-treatment left knee MRI demonstrated grad I-II damage of patellar cartilage, grade III damage of posterior horn lateral meniscus, grade I damage of ACL, and mild degenerative changes.

Table 4. Functional Rating Index (FRI) and Visual Analog Score (VAS) walking index.

Patients	Outcome measures	Pre-treatment	3 Months post	9 Months post
Patient 1	FRI	10	0	0
	VAS	7	0	0
	R.O.M	0°-140°	0°-155°	0°-155°
Patient 2	FRI	16	6	4
	VAS	8	5	0
	R.O.M	5°-120°	0°-135°	0°-140°
Patient 3	FRI	11	4	0
	VAS	6	0	0
	R.O.M	5°-135°	0°-145°	0°-145°

Patient 2

The patient is 57-year-old male presented with right knee pain since 3 years. He had daily pain score 6/10 increased to 8/10 with daily activities. On physical examination, right knee McMurray test were positive with locked knee, range of motion as in **Table 4**. Pre-treatment MRI showed right knee medial and lateral meniscus injury with osteoarthritis changes.

Patient 3

The patient is 60-year-old male presented with left knee pain since 5 months, he had history of left knee trauma since he was 20-year-old. He had a daily pain score 4/10 increased to 6/10 with daily activities. On physical examination, left knee McMurray test was positive with locked knee, range of motion as in **Table 4**. Pre-treatment MRI showed left knee medial meniscus injury, patellar chondromalacia and early osteoarthritis changes.

Materials and methods

One week prior to Pre-SVF arthroscopy procedure, the patients was restricted from taking corticosteroids, NSAIDs, and aspirin.

The patients were placed supine on OR table, a standardized protocol for general anesthesia was followed. Abdominal towel was placed after painting the abdominal area. Then, patient 1 had two incisions of approximately 0.5cm were made approximately 15cm on right and left sides of the umbilicus, while patient 2 and patient 3 had one incision of approximately 0.5cm were made 3cm infra-umbilicus. tumescent solution was injected (1000 cm³ normal saline, 10 cm³ ropivacaine, 20 cm³ lidocaine, 0.5 cm³ epinephrine). Then using 3.5 cannula extracting a total of 450 cm³ of lipoaspirate, which resulted in total of 250 cm³ adipose tissue separated by gravity. The adipose tissue was sent for processing, and arthroscopy procedure began.

Arthroscopy

The arthroscopic surgery was performed, medial and lateral meniscus was explored interiorly, partially excised and smoothened in a special technique to keep the structure of the meniscus, which aim to minimally trimming of the inferior part of the injured area of the meniscus, maintaining the scaffold and the shape of the meniscus. The intra-articular tube was then applied, incision is sutured, crepe bandage was applied. The adipose derived stem cell mixture was then injected via tube, and then tube is removed. Hinged knee support was applied.

ADSC processing

The resulting 250 cm³ of adipose tissue was centrifuged at 700 RCF for 5 minutes. Which result approximately 180 cm³ of packed adipose tissue, fibrous tissue, red blood cells, and small amount of nucleated cells. Then, ADCs were extracted by the use of digestive enzymes, collagenase type I derived from *Clostridium histolyticum* (SERVA; Heidelberg, Germany), and mixed with the centrifuged lipoaspirate at ratio of 1:1 and digested for 30 minutes at 37°C while rotating [45]. After digestion, the lipoaspirate was separated of the enzyme by centrifugation at 800 RCF for 5 minutes, the separated enzyme was then removed. The lipoaspirate were then washed 3 times to remove the collagenase, and the lipoaspirate were centrifuged at 800 RCF after each wash. Finally, approximately 6 cm³ of ADSCs were obtained after the last centrifuge process.

While preparing the ADSCs, 49 cm³ of autologous blood was drawn with 14 cm³ of anticoagulant mixture (ACD-A), then centrifuged at 1700 RCF for 5 minutes. Then, the supernatant was drawn and discarded. Obtained is 4 cm³ PRP. The PRP was activated by mixed with CaCl₂ at a ratio of 10:1 (PRP 10:1 CaCl₂). Hyaluronic acid 3 cm³ was added to act as a scaffold.

After obtaining the ADSCs mixture and PRP, the mixture was injected via the intra-articular tube, and then tube was removed, the patient referred from recovery room to the ward. After discharged, the patient was told to maintain activity as tolerated.

The patient returned in the days 3, 7, 14 of the first procedure for additional three PRP injections and one HA injection.

Result

The patients had follow-up after the treatment in six months and nine months, their symptoms have significantly improved, modified functional rating index and visual analog score walking index [50,51] showed in Table 4. While follow-up, the patients were observed if symptoms improvement persistent, develop any complications (e.g., illness, infection), and if developed any form of cancer since the procedure. The patient did not report any of these complications or serious side effects, a recent report supports this result [30]. Repeated MRI after 6~9 months showed significant regeneration of the torn meniscus, and thickness in the articular cartilage (Figures 1-3).

It is estimated that approximately 400,000 ADSCs are obtained in one gram of adipose tissue [52]. And since 180 grams of centrifuged adipose tissue were obtained, it is believed that approximately 72 million adipose derived stem cells were injected into the patient's knee.

Discussion

This clinical case report provides MRI evidence before and after ADSCs treatment, the significant signal changes can be interpreted as sign of restored and regenerated meniscus. MRI results can be compared with sequential views to compensate any possible errors. The findings of the present study demonstrates that adipose-derived stem cell is effective in cartilage healing, reducing pain, and improving joint func-

Figure 1. Patient 1 MRI sagittal and coronal views of the left knee. Pre-treatment MRI scan demonstrate a tear within the posterior horn lateral meniscus in sagittal view (A) and coronal view (B). Post-treatment MRI scan at 6 months demonstrate the healed meniscus, increased thickness of articular cartilage, as well as improved quality of the articular cartilage in sagittal view (C) and coronal view (D) which been regenerated and repaired by the Pre-SVF arthroscopy treatment.

Figure 2. Patient 2 Pre-treatment MRI scan demonstrate grade-III tear within the anterior horn medial meniscus in sagittal view (A). Post-treatment MRI scan at 9 months demonstrate the healed meniscus in sagittal view (B). Pre-treatment MRI scan demonstrates tear within the posterior horn medial meniscus (Yellow arrow) and anterior horn medial meniscus (Red arrow) in sagittal view (C). Post-treatment MRI scan at 9 months demonstrate the healed anterior and posterior medial meniscus in sagittal view (D). Pre-treatment MRI scan demonstrates articular cartilage thickness in sagittal view (E). Post-treatment MRI scan at 9 months demonstrate increased thickness and quality of articular cartilage in sagittal view (F).

tion of patients with meniscus tear and knee OA. However, there is no way to determine the nature of the regenerated tissue without biopsy. Longer term follow up of this patient will continue.

There are few possible mechanisms of the regenerative meniscal and cartilage: (i) direct differentiation of ADSCs [45,53-74]; (ii) paracrine effects of ADSCs on the existing tissue [75-91]; (iii) the growth factors contained in PRP [92-99], which also may stimulate the injected stem cells to proliferate and differentiate [100,101]; Or (iv) combination of previously mentioned possibilities. According to this clinical study, and

Figure 3. Patient 3 Pre-treatment MRI scan demonstrate grade-III tear within the posterior horn medial meniscus in sagittal view (A). Post-treatment MRI scan at 6 months demonstrate the healed meniscus in sagittal view (B). Pre-treatment MRI scan demonstrates degenerative changes within the medial meniscus body coronal view (C). Post-treatment MRI scan at 6 months demonstrate regenerative changes within the medial meniscus body and articular cartilage in coronal view (D).

previous clinical reports [32-37,40,102], it is found that ADSCs mixture-based treatment play an important role in repair the cartilage and torn meniscus.

The limitation of the present study that there is no control group was included, in order to measure the effectiveness and compare results of patients that have similar symptoms and absolute indication of arthroscopy, future studies will compare these patients results with Pre-SVF arthroscopy treatment (for the group of patients who are willing to proceed with arthroscopy) and control group (SVF without arthroscopy for patients who are unwilling to proceed with arthroscopy, or arthroscopy without SVF for patients who are unwilling to proceed with SVF).

Competing interests

The author declares that he has no competing interests.

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