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Evaluating the Effects on Ultrasound and on Magnetic Resonance for Knee Osteoarthritis Treatment by Platelet Rich Plasma Therapy in Combination with Mesenchymal Stem Cells from Autologous Adipose Tissue

Truong Sinh Cao, Tuan Nguyen Viet

Vinh Medical University Hospital, Vinh City, Vietnam
Email: caotruongsinh@gmail.com, drhope.vmu@gmail.com

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Abstract

Aim: To evaluate the effects based the changes on ultrasound and on magnetic resonance for knee osteoarthritis treatment by platelet-rich plasma therapy in combination with mesenchymal stem cell from autologous adipose tissue. **Objects and Methods:** 30 patients, 26 females, 4 males, mean age 58.63 ± 11.11, mean disease duration 5.3 ± 4.6 years, respectively 60 knee joints were diagnosed with osteoarthritis at stage II - III according to the Kellgren and Lawrence classifications. After ultrasound and magnetic resonance imaging in the first time, all patients were injected with platelet-rich plasma combined with mesenchymal stem cells from autologous adipose tissue into both knee joints. **Results**: After treatment 12 months by platelet-rich plasma injection combined with mesenchymal stem cells from autologous adipose tissue: The thickness of articular cartilage on ultrasound increased significantly from 2.08 ± 0.36 mm to 2.48 ± 0.36 mm with $p < 0.05$. There were 52 joints with increased cartilage thickness, equivalent to 86.67%. The surface of articular cartilage on magnetic resonance in all positions of the knee joint has improved, the difference was statistically significant. Particularly, the patellar joint improved from 1.56 ± 0.25 mm to 1.64 ± 0.21 mm with $p < 0.05$. **Conclusion:** The treatment of knee osteoarthritis by platelet-rich plasma combined with mesenchymal stem cells from autologous adipose tissue was effective in improving cartilage thickness on ultrasound and magnetic resonance, thereby improving the motor function of the knee joint.

Keywords

Platelet-Rich Plasma, Mesenchymal Stem Cells, Osteoarthritis, Ultrasound, Magnetic Resonance

1. Introduction

Knee osteoarthritis is the second leading cause of disability in the elderly after cardiovascular disease. Osteoarthritis of the knee most affects mobility. Severe knee osteoarthritis is the cause of disability for many patients, increasing the medical costs of the family and society.

Currently, there are a number of new methods in the treatment of knee osteoarthritis, including the method of using autologous platelet-rich plasma, stem cells and combining plasma with stem cells.

Autologous intra-articular platelet-rich plasma (PRP) injection is a new method in the treatment of osteoarthritis. Platelet-rich plasma has been shown to contain growth factors, in which, transforming growth factor-β (TGF-β) plays an important role to increase the base for chondrocytes' growth, the proliferation of chondrocytes and the regulation of proteoglycan synthesis [1].

In the world, in the past few years, many studies have shown that autologous intra-articular PRP injection is an effective therapy in the treatment of knee osteoarthritis [2]. This has been proven by many studies around the world.

Mesenchymal stem cells (MSCs) have the potential for self-renewal and multidirectional differentiation [3] which can exert therapeutic effects on various diseases through directed differentiation [4], regulate immune system [5], anti-inflammatory, progenitor [6], improve microenvironment [7] and promote regeneration [7]. MSCs have been used in the treatment of various diseases [8], such as ovarian failure, Parkinson's disease, nervous system damage and amyotrophic lateral sclerosis (ALS). MSCs therapy can be applied in the treatment of knee osteoarthritis and has shown encouraging results [4] [8].

Recent researches have shown the presence of stem cells in adipose tissues which are known as adipose-derived stem cells (ADSCs). These cells are referred to as mesenchymal stem cells (MSCs) that expose a number of special characteristics. They participate in the fibroblast-like surface formation and differentiate into osteoblasts, cartilage, and adipocytes [9]. Many researches have been conducted over the last few years which include preclinical and clinical trials to perform the treatment of cartilage injuries and knee osteoarthritis.

Stem cell therapy is a milestone in regenerative medicine for the treatment of knee osteoarthritis. MSCs have not been widely adopted because of cell source problems and expensive cell cultures. Furthermore, its efficacy and safety are being explored [10].

Therefore, the combination therapy of platelet-rich plasma with mesenchymal stem cells from autologous adipose tissue will promote both types of effects: 1)

TGF-β plays the role of increasing the substrate for chondrocyte's growth, proliferation of chondrocytes, regulation of proteoglycan synthesis; 2) mesenchymal stem cells increase cartilage regeneration, repair the organization of damaged cartilage, regenerate subchondral bone to heal joints.

To implement treatment, evaluate the effects of platelet-rich plasma and mesenchymal stem cells on articular cartilage, we conducted a topic with the aim of: "Evaluating results based on ultrasound and magnetic resonance of Treatment of knee osteoarthritis with platelet-rich plasma in combination with mesenchymal stem cell transplantation from autologous adipose tissue.

2. Objects and Method

2.1. Study Setting and Design

The research is an intervened study which evaluates the effects by comparing those before and after treatment 12 months based onchanges ofuntrasoud and changes of cartilage thickness on magnetic resonance images.

The study was implemented at Vinh Medical University Hospital, from June 2020 to February 2021.

2.2. Study Population

In the study, there are selected 30 patients including 26 females and 4 males; correspondingly, 60 knee joints were diagnosed with osteoarthritis according to the American College of Rheumatology (ACR) who are at the mean age of 58.63 ± 11.11, disease duration is from 5.3 ± 4.6 years which is respectively of stages II - III according to the classification standard of Kellgren and Lawrence with a normal platelet count (≥150,000/mm^3).

The inclusion criteria:

- This design is excluded patients who were diagnosed osteoarthritis according to the classification standard of Kellgren and Lawrence.
- The platelet count of patientswas normal (≥150,000/mm^3).

The exclusion criteria:

- The patients were at stage I, stage IV of knee osteoarthritis;
- The patients havesevere anemia and platelets <150,000/mm^3
- The patients have the secondary knee osteoarthritis, post-traumatic of knee joint, infectious degeneration of knee joint and the patients with cancer or have contraindications to surgery.

Patients received ultrasound and magnetic resonance imaging to evaluate input data before injecting platelet-rich plasma in combination with mesenchymal stem cells from autologous adipose tissue.

All patients were fully explained the benefits, possible side effects, consented to participate the study, which was performed in accordance with the Helsinki declaration. This technique was allowed by Viet Nam Ministry of Health. The study protocol was approved by the Scientific and Ethical Council of Vinh Medical University Hospital.

2.3. Study Materials

Autologous platelet-rich plasma was extracted from 30 ml of peripheral blood according to the process of PRP set, APC 30 PRP PRCEDURE PRAK and the Harvest smart extraction system of TERUMO BCT-USA, following an 8-step process with a count of 5ml (platelet count is up to 1.5 milliion/ml).

Autologous mesenchymal stem cells were obtained from the patient's abdominal adipose tissue and was extracted by a set of ADI-25-01 ADIPOSEPRCEDURE PRAK (2 syringes, 25 ml in each syringe) and by the Harvest Smart Stem Cell Extractor of TERUMO BCT-USA company according to the 10-step process, the obtained count is 10 ml with 1.6 milion cells.

Two products with platelet-rich plasma and stem cells were mixed together (15 ml) and then were equally divided into 2 single-use syringes, each 7.5 ml syringe was injected into a knee joint.

All procedures are carried out in the operating room, extraction room, and sterile injection room.

2.4. Criteria for Evaluating Treatment Results

1) Evaluating the results on ultrasoud after tratment 12 months, comparison with before treatment. Including:

- Effusion level of knee joint before and after treatment 12 months.
- The thickness of articular cartilage (mm) before and after treatment 12 months including 3 sites: intercondylar, internal condyle, external condyle.

2) Evaluating the results on magnetic resonance image after 12 months of follow-up in comparison with before treatment. Including:

- There is a number of patients with changes in cartilage thickness on magnetic resonance image.
- The cartilage thickness is changed after treatment: the thickness of articular cartilage is measured at the positions of internal condyle, external condyle of the femur, intercondylar, medial tibial plateau, lateral tibial plateau, middle tibial plateau, patella.

2.5. Statistical Analysis

The data was processed using SPSS 20.0 software; qualitative variables are expressed as frequency and proportions, quantitative variables are expressed as mean ± standard deviation. The Chi^2 test was used to compare the 2 proportions and the T test was to compare the 2 means. The difference was statistically significant when $p < 0.05$.

3. Results

3.1. Baseline Characteristics

In this study sample, the number of male patients including 4 people accounted for 13.3% and the number of joints with stage III damage accounted for 80%. The results showed in Table 1.

Table 1. Baseline characteristics.

Variable	Male	Female	Total
Number of patients	4 (13.3%)	26 (86.7%)	30 (100%)
Number of joints	8 (13.3)	52 (86.7)	60 (100%)
Age	54.25 ± 9.57	59.31 ± 11.34	58.63 ± 11.11
Disease duration	3.00 ± 1.15	5.69 ± 4.88	5.3 ± 4.6
Height	1.63 ± 0.03	1.55 ± 0.05	1.56 ± 0.05
Weight	64.25 ± 7.27	53.5 ± 7.2	54.93 ± 8.00
BMI (kg/m^2)	24.0 ± 2.33	22.1 ± 2,2	22.3 ± 2.28
Obesity	0	2 (6.7%)	2 (6.7%)
Diabetes	1 (3.3%)	2 (6.7%)	3 (10%)
Hypertension	2 (6.7%)	4 (13.3%)	6 (20%)
Degenerative stage according to Kellgren and Lawrence classification			
Stage II	2 (3.3%)	10 (16.7%)	12 (20%)
Stage III	6 (10%)	42(70%)	48 (80%)
Platelet count	220.25 ± 53.7	275.23 ± 90.44	267.9 ± 87.81

3.2. Evaluating the Results Based on Ultrasoud

The rate of patients with knee effusion decreased from 56.7% (17/30) to 40% (12/30) after treatment 12 months, left kneejoint decreased from 66.7% (20/30) to to 33.3% (10/30) after treatment 12 months. Moderate and multiple knee joint effusion levels on ultrasound of both knee joints had a significant improvement with $p < 0.05$. The results were presented in Table 2.

The thickness of articular cartilage on ultrasound increased significantly from 2.08 ± 0.36 mm to 2.48 ± 0.36 mm after treatment 12 months ($p < 0.05$). There was an improvement in articular cartilage thickness in all 3 condylar positions. The date were showed in Table 3.

3.3. Evaluating the Results Based on the Changes of Cartilage Thickness on Magnetic Resonance

The surface of articular cartilage on magnetic resonance in the above mentioned positions were improved after 12 months of treatment, the difference was statistically significant. The results were presented in Table 4.

After 12 treatment months, there were 8 joints (13.33%) that did not change the total thickness of cartilage at the measured locations (lower end of femur, upper end of tibial, patella joint), found in degenerative joints of stage III. The date were showed in Table 5.

4. Discussion

4.1. Evaluation of Treatment Results on Ultrasound

Currently, ultrasound is widely used in the diagnosis and treatment of musculoskeletal diseases. The results of our study in Table 2 showed that: The patient

Table 2. Evaluating the results by the levels of joint effusion on ultrasound.

Effusion level (mm)	Right knee joint					Left knee joint				
	BT		AT		p(b-a)	BT		AT		p(b-a)
	n	%	n	%		n	%	n	%	
No effusion	13	43.3	18	60.0	<0.05	10	33.3	20	66.7	<0.05
Effusion										
< 5 mm (1)	6	20.0	9	30.0		6	20.0	8	26.7	
5 - 10 mm (2)	5	16.7	2	6.7		12	40.0	2	6.6	
>10 mm (3)	6	20.0	1	3.3		2	6.7	0	0	
Total (1-3)	17	56.7	12	40.0	<0.05	20	66.7	10	33.3	<0.05
General total	30	100	30	100		30	100	30	100	

BT = Before treatment; AT = After treatment; p(b-a): P value before-after treatment.

Table 3. Evaluating the results based on the thickness of articular cartilage on ultrasound.

Articular cartilage thickness (mm)	BT (mm)	AT 12 months (mm)	p(b-a)
Intercondylar	2.33 ± 0.56	2.71 ± 0.46	<0.05
Medial condyle	1.89 ± 0.45	2.31 ± 0.53	<0.01
Lateral condyle	2.01 ± 0.51	2.40 ± 0.46	<0.05
Chung	2.08 ± 0.36	2.48 ± 0.36	<0.05

Table 4. Changes in thickness of articular cartilage on MRI.

Position	Time	Measurement position (mm)					
		External condyle	p(b-a)	Internal condyle	p(b-a)	Intercondylar	p(b-a)
Lower end of femur	Before treatment	1.40 ± 0.10	0.00	1.35 ± 0.16	0.00	1.57 ± 0.11	0.00
	Aftertreatment	1.46 ± 0.11		1.42 ± 0.15		1.64 ± 0.12	
Upper end of femur	Before treatment	1.39 ± 0.10	0.00	1.35 ± 0.16	0.00	1.56 ± 0.12	0.00
	After treatment	1.45 ± 0.12		1.43 ± 0.16		1.63 ± 0.12	
Patellofemoral joint	Before treatment			1.56 ±0.09			0.00
	After treatment			1.65±0.09			

p(b-a): p-value before and after treatment.

Table 5. Number of joints with changes in cartilage thickness on MRI.

Variabilities	Stage II		Stage III		Overall	
	n	%	n	%	n	%
Unchanged joints	0	0	8	100	8	13.33
Changed joints	12	23.07	40	76.92	52	86.77

percentage with knee effusion decreased from 56.7% to 40% after 12 months of treatment, and the left knee joint decreased from 66.7% to 33.3% after 12 months of treatment. Moderate joint effusion, much on ultrasound both knee joints has markedly improved.

Many authors have considered the parameters of articular cartilage thickness on ultrasound as an effective parameter to diagnose and evaluate the progression of degenerative joint disease. In this study, we conducted to measure the cartilage thickness of the lower femoral end at 3 locations: the internal condyle, the external condyle and the intercondylar. The results showed that there was a statistically significant improvement in articular cartilage thickness in all 3 positions of the external condyle, the internal condyle and the intercondylar. The average thickness of articular cartilage on ultrasound after 12 months increased from 2.08 ± 0.36 mm to 2.48 ± 0.36 mm (**Table 3**). Thus, there was a clear improvement in articular cartilage thickness after treatment 12 months.

Toghraie F *et al.* (2012) conducted a study on adipose tissue stem cells taken from subcutaneous fat to treat knee osteoarthritis at 28 New Zealand white rabbits. This authors group induced osteoarthritis in rabbits by transverse anterior cruciate ligament. In terms of cytology, cartilage quality in the study group improved over time in terms of cartilage structure, thickness and surface [11].

Chris Hyunchul Jo *et al.* (2014) conducted a survey on the efficacy and safety when injecting adipose tissue stem cells for 18 patients with stage II knee osteoarthritis and above according to Kellgren and Lawrence. All patients underwent endoscopic diagnosis before treatment, classified by the International cartilage repair society (ICRS International cartilage repair society). Histopathologically, the biopsy specimen at the condyle in the femoral bone did not have articular cartilage before treatment. After 6 months, it was observed that the articular cartilage was regenerated with the characteristic of thick, white, shiny cartilage with smooth surface, with the expression of type II collagen after staining and fusion with the subchondral bone [12].

4.2. Evaluation of Treatment Results on Magnetic Resonance

The change of articular cartilage thickness on magnetic resonance was an important parameter to evaluate the therapeutic effect by mesenchymal stem cells combined with platelet-rich plasma because stem cells increase cartilage regeneration. Platelet essence factor stimulates cartilage production.

The results in **Table 4** in our study showed that 52/60 joints (86.67%) had a change in cartilage thickness after treatment 12 months. The remaining 8 joints remained unchanged, in 4 patients, possibly due to age, long degeneration time and severe damage in stage III.

About the degree of change: In our study, there was an improvement in the surface of articular cartilage on magnetic resonance in all positions. At the position of the lateral condyle of the lower femoral head increased from 1.39 ± 0.10 mm before treatment to 1.46 ± 0.11 mm after treatment 12 months. In the posi-

tion of the medial condyle in the lower femoralend increased from 1.35 ± 0.14 mm to 1.42 ± 0.14 mm, the position of the condyle in the head of the tibia increased from 1.35 ± 0.14 mm to 1.44 ± 0.15 mm after treatment 12 months. The position of the inferior femoral condyle increased from 1.57 ± 0.11 mm to 1.65 ± 0.12 mm after treatment 12 months. The supracondylar intercondylar position increased from 1.56 ± 0.12 mm to 1.64 ± 0.12 mm after 12 months of treatment. At all 3 measurement positions of the knee joint, there was an improvement from 1.56 ± 0.25 mm to 1.64 ± 0.21 mm after treatment 12 months (**Table 4**). **Table 4** shows that after treatment 12 months, there were 8 stage III joints (13.33%) with no change in total cartilage thickness at measurement sites such as lower femoral end, upper tibia and patellar joint. This result is similar to the research results of many domestic and international authors.

Investigation of the treatment effectiveness through the parameters on magnetic resonance was applied by many authors in evaluating the effectiveness of autologous adipose tissue stem cell therapy or platelet-rich plasma therapy in the treatment of degenerative diseases knee joint.

Khanh Hong Thien Bui *et al.* (2013) conducted a study on 21 patients with stage II-III knee osteoarthritis treated by adipose tissue stem cell therapy combined with platelet-rich plasma. After 8.5 months of treatment, the analysis on magnetic resonance showed that there was cartilage regeneration at the damaged sites. The thickness of articular cartilage was thicker after 6 months of treatment [13].

Research by author Tien Tran Viet *et al.* in 2016 showed that there was an improvement in articular cartilage thickness on magnetic resonance in 4 positions of the medial tibial plateau, lateral tibial plateau, medial condyle and lateral condyle of the femur at time, score after 6 months and 1 year of follow-up but not statistically significant ($p > 0.05$). This may be because the majority of the study subjects are mild knee osteoarthritis (stage I-II), so the difference is not clear [14]. This study also uses the Circularity index: an index to assess the degree of smoothness of the cartilaginous surface. If the cartilage is worn away, the cross-sectional area decreases and the cross-sectional circumference becomes longer, so the roundness of the cartilage decreases. The results showed that the Circularity index increased during the follow-up period, significantly different from the control group ($p < 0.05$), which shows that the damage repair role is diffuse in the injury site [14].

In 2017, Thu Pham Hoai studied the results of treating primary knee osteoarthritis with autologous adipose tissue stem cell therapy, the author found that: The thickness of articular cartilage at the femoral condyle increased from 1, 52 ± 0.57 mm before treatment to 1.61 ± 0.59 mm after 6 months and after 1 year of treatment is 1.65 ± 0.56 mm, articular cartilage thickness at the tibial plateau from 1.59 ± 0.59 mm before treatment, after 6 months of treatment is 1.68 ± 0.59 mm and after 1 year is 1.75 ± 0.57 mm [15].

In 2012, the author Yong-GonKoh and colleagues conducted a study to eva-

luate the clinical and imaging results in 18 patients with knee osteoarthritis treated with autologous adipose tissue stem cells collected in the lower part of the body patella. Evaluation of the improvement of articular cartilage by the whole organ magnetic resonance imaging score (WORMS) showed that the WORMS score decreased from 60.0 to 48.3 points ($p < 0.01$). In particular, this study also showed that there is a positive correlation between the improvement of clinical symptoms and images of knee osteoarthritis with the amount of TBG injected. The study authors concluded that adipose tissue stem cells are a valuable source of cells in the treatment of articular cartilage damage [16].

Chris Hyunchul Jo et al in 2014 conducted a survey on the efficacy and safety of adipose stem cell injection for 18 patients with stage II knee osteoarthritis and above according to Kellgren and Lawrence. The team found no change in the degree of degeneration according to Kellgrence and Lawrence, joint space narrowing, mechanical axis and anatomical axis after 6 months of treatment with these 3 doses. However, observations on magnetic resonance showed that there was a recovery of articular cartilage over time in the medial condyle and medial tibialplateau after 6 months of treatment. The size of articular cartilage damage on magnetic resonance decreased statistically significantly at all sites except for the patella in the treated group. The volume of articular cartilage at the site of the lateral condyle, the lateral tibial plateau and the patella remained unchanged at all doses after 6 months. The study concluded that intra-articular injection of autologous adipose tissue stem cells with a dose of 1x108 stem cells in patients with knee osteoarthritis improves pain and function of the knee joint without causing any complications, reducing the area of damaged articular cartilage by the hyaline-like cartilage regeneration pathway [17].

Liang-jing Lu and colleagues (2016) reported a study on 18 patients with bilateral knee osteoarthritis who were treated with 3 injections of adipose tissue stem cell therapy: before treatment, after 3 weeks and after 48 weeks, showed that the volume of cartilage of the femur, tibia and patella increased steadily during the entire follow-up period, which was statistically significant at the time of 6 months, 12 months and 18 months [12].

The authors' results showed that adipose tissue stem cells were effective in repairing articular cartilage damage.

5. Conclusion

The treatment of knee osteoarthritis by platelet-rich plasma combined with mesenchymal stem cells from autologous adipose tissue was effective in improving cartilage thickness on ultrasound and magnetic resonance, thereby improving motor function, movement of the knee joint.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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