EFFICACY OF PLATELET-RICH PLASMA INTRA-ARTICULAR INJECTION IN ADJUNCTION TO CONVENTIONAL THERAPY FOR ASEPTIC NECROSIS OF FEMORAL HEAD

Le Thuy Duong[1], Luu Thi Binh[2], Nguyen Minh Nui[3]

Summary

Objectives: To evaluate the results of autologous platelet-rich plasma (PRP) intra-articular injection combined with medical therapy in treating aseptic necrosis of the femoral head (ANFH) after 5 months. ***Subjects and methods:*** Non-control interventional study, comparing before and after treatment for 30 patients (47 sterile necrotic femoral heads) who received 2 injections of PRP one month apart. Evaluation of clinical symptoms and images of necrosis on magnetic resonance imaging of the hip joint after 5 months. ***Results:*** The mean Visual Analogue Scale (VAS) decreased from 7.03 ± 1.90 to 3.77 ± 2.64, and the rate of severe pain decreased from 63.3% to 23.3%. The average range of motion of the hip joint increased (flexion from 87.17 ± 13.69 to 101.50 ± 14.69; abduction from 21.50 ± 5.89 to 28.50 ± 7.09; external rotation from 28.33 ± 4.01 to 34.00 ± 5.15; internal rotation from 30.33 ± 4.90 to 34.17 ± 4.93 degrees) with $p < 0.001$. According to Merle D'Aubigné, the ability to walk score increased from 4.05 ± 0.83 to 4.95 ± 0.76 ($p < 0.001$). Magnetic resonance imaging showed the rate of bone marrow edema decreased from 66.7% to 40.0% ($p < 0.05$), four sterile necrotic femoral heads from stage III to stage IV. ***Conclusion:*** The results of autologous PRP intra-articular injection combined with medical therapy in treating ANFH have markedly improved analgesia and motor function.

** Keywords: Aseptic necrosis of the femoral head; Platelet-rich plasma.*

[1]Hai Phong Medical College

[2]Thai Nguyen Province Health Department

[3]Vietnam Military Medical University

Corresponding author: Le Thuy Duong (bs.duongle2023@gmail.com)

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INTRODUCTION

Aseptic necrosis of the femoral head is caused by an interruption of the blood supply to the femoral head (FH). The necrotic part of the bone below the cartilage of the femoral head will collapse the spherical structure of the upper articular cartilage. The end result of this process is secondary hip osteoarthritis, loss of function of the hip joint, leading to disability. As osteoarthritis progresses, the patients will often need a total hip replacement. In the United States, more than 10,000 new patients are affected with the disease every year, and it accounts for up to 10% of total hip arthroplasties [1]. Current medical treatment is limited, mainly pain relievers, anti-inflammatory, and anti-osteoporosis, reducing the symptoms of the disease. The conservative methods of ANFH are decompression drilling and bone grafting, and studies have shown improved outcomes with the combination of PRP intra-articular injections. This method is based on the principle that PRP contains growth factors that stimulate regeneration, anti-inflammatory and analgesic, so it has been used in the treatment of osteoarthritis and soft tissue diseases around the joints. In the world, medical treatment of ANFH combined PRP intra-articular injection was first reported in 2012 and showed significant improvement in pain, hip mobility, ultrasound images, and magnetic resonance after one month [2].

Therefore, to confirm the therapeutic effect of PRP, we carried out the study: *To evaluate the results of medical treatment combined with autologous PRP injection after 5 months in patients with ANFH in Vietnam.*

SUBJECTS AND METHODS

1. Subjects

47 femoral heads (30 patients with confirmed ANFH) were eligible for combined treatment with autologous platelet-rich plasma at E Hospital and Thai Nguyen National Hospital from January 2017 to October 2022.

* *Inclusion criteria*: Patients with aseptic necrosis of FH stages I, II, III, IV according to ARCO (1993) classification [3].

* *Exclusion criteria*: Blood hemoglobin less than 110 g/l, blood platelets less than 150 g/l, coagulopathy, hemodynamic instability; systemic diseases.

2. Methods

* *Research design*: Prospective, comparing results before and after treatment.

* *Sample size*: Convenience sampling.

During the study, we selected 47 FHs (30 patients) who applied combined treatment with autologous PRP.

- The patient received medical treatment for ANFH, including: Eliminating risk factors, reducing leg pain, exercising joint exercises, relieving pain with NSAID or Paracetamol, Bisphosphonate, calcium supplement, vitamin D, and treatment of comorbidities.

- Combined treatment with autologous PRP intra-articular injection

+ Patients stopped using NSAID within 48 hours before PRP injection treatment.

+ Using PRP extracted by PATCO's Tricell kit (available at Pharmacy Departments of E Hospital and Thai Nguyen National Hospital). Patients were taken 30 mL of venous blood. The blood samples were centrifuged for 5 minutes at 3,200 revolutions per minute (r.p.m). Then, the samples were centrifuged at 3,300 r.p.m for another 3 minutes to get 4 mL of PRP. The technique of intra-articular injection of PRP under ultrasound guidance was performed by musculoskeletal specialists at an aseptic procedure room for 1 dose/month x 2 injections.

- Patients were evaluated at 3 time points: Before the first injection of PRP (T_0), before the 2nd PRP injection (T_1), and 5 months after the second injection (T_2).

- Clinical assessment at time points T_0, T_1 and T_2.

+ Pain level according to VAS (severe pain ≥ 7 points; moderate pain: 4 - < 7 points; mild pain: 1 - < 4 points; no pain: 0 points).

+ Range of motion (ROM) of the hip joint: Flexion, abduction, external rotation, internal rotation.

+ Ability to walk score according to Merle D'Aubigné: 1 - 3 points: Very limited (1 point: Only with crutches, 2 points: Only with two canes, 3 points: Limited with one cane, very difficult without a cane); 4 - 5 points: Slight limitation (4 points: Prolonged with one cane, limited without a cane, 5 points: Without a cane but slight limp); 6 points: Normal [4].

- Evaluation of lesion images on magnetic resonance film at time point T_0 and T_2 performed by Doctor - Radiology specialist of E Hospital and Thai Nguyen National Hospital. Method of hip arthroplasty using pulse sequences: Coronal or sagittal T1W, coronal or sagittal T2W, coronal STIR, and axial T1W.

+ The lesion area of signs of necrosis (hypointensity on T1-weighted images), subchondral fractures, and surface collapse were divided into levels ≤ 15%, 15 - 30%, and > 30% according to the ARCO (1993) classification.

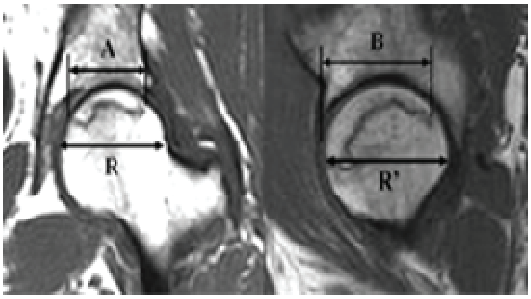

Figure 1: Calculating % of lesion area.

** Source: According to David R. Steinberg (2006)*

Calculation:

* % lesion area = (A x B/R x R') x 100

In which:

R: The maximum diameter of the FH in the coronal section.

R': The largest diameter of the FH on the sagittal section.

A: Maximum length of the necrotic area in coronal view.

B: Maximum length of the necrotic area in sagittal view.

+ Double-line sign: Yes or no.

+ Bone marrow edema: Yes or no.

+ Effusion: According to Mitchell's classification [5].

+ Disease stage: According to the classification of ARCO (1993) [3].

This method of treatment was conducted with the permission of E Hospital and Thai Nguyen National Hospital.

** Statistical analysis:*

Data were analyzed using the SPSS, version 16.0. Descriptive statistics were used to present the patient characteristics. The normally distributed data were presented as means ± standard deviations (SDs). Descriptive statistics utilized $\chi 2$ for categorical measures and t-test for continuous measures. A p-value less than 0.05 was considered statistically significant.

RESULTS

1. Patient characteristics

Table 1: Patient characterisstics.

Clinical characteristics		Number of patients (n = 30)	Rate (%)
Median age: years		53.83 ± 11.46 (30 - 73)	
Gender	Male	21	70.0
	Female	9	30.0
Number of necrotic femoral heads/patient	Unilateral	13	43.3
	Bilateral	17	56.7

Male patients were more than female, and most of the femoral head necrosis was bilateral.

2. Results of medical treatment combined with autologous PRP injection

Table 2: Evaluation of the results of pain relief, improvement of movement, and walking ability before and after the 1st PRP injection.

Characteristics \ Time point		T_0 n, (%)	T_1 n, (%)	p
Pain level according to VAS (n = 47 FHs)	Severe	33 (70.2%)	12 (25.5%)	-
	Moderate	12 (25.5%)	27 (57.4%)	
	Mild	2 (4.3%)	8 (17.0%)	
	Mean VAS score	7.28 ± 1.74	5.38 ± 1.03	< 0.001
Hip ROM (degree) (n = 47 FHs)	Flexion	83.83 ± 16.09	95.00 ± 14.71	
	Abduction	20.32 ± 5.75	26.60 ± 6.92	
	External rotation	28.09 ± 4.11	32.23 ± 4.27	
	Internal rotation	29.68 ± 4.59	33.51 ± 4.16	
Ability to walk (n = 30 patients)	Very limited	10 (33.3%)	6 (20.0%)	-
	Slight limitation	20 (66.7%)	20 (66.7%)	
	Normal	0 (0.0%)	4 (13.3%)	
	Mean Merle D'Aubigné Score	3.67 ± 1.09	4.53 ± 1.20	< 0.001

The results of pain reduction, improvement of movement, and walking ability were markedly improved in T_1 compared to T_0 with $p < 0.001$.

Table 3. Evaluation of the results of pain relief, improvement of movement, and walking ability before and after the 2nd PRP injection.

Characteristics \ Time point		T_1 (n, %)	T_2 (n, %)	p
Pain level according to VAS (n = 30 FHs)	Severe	5 (16.7%)	7 (23.3%)	-
	Moderate	17 (56.7%)	7 (23.3%)	
	Mild	8 (26.7%)	12 (40.0%)	
	No pain	0 (0.0%)	4 (13.3%)	
	Mean VAS score	4.67 ± 1.89	3.77 ± 2.64	< 0.01
Hip ROM (degree) (n = 30 FHs)	Flexion	98.83 ± 10.80	101.50 ± 14.69	> 0.05
	Abduction	28.17 ± 5.33	28.50 ± 7.09	> 0.05
	External rotation	32.83 ± 4.09	34.00 ± 5.15	
	Internal rotation	34.33 ± 4.30	34.17 ± 4.93	
Ability to walk (n = 20 patients)	Very limited	2 (10.0%)	1 (5.0%)	
	Slight limitation	15 (75.0%)	15 (75.0%)	
	Norman	3 (15.0%)	4 (20.0%)	
	Mean Merle D'Aubigné Score	4.90 ± 0.79	4.95 ± 0.76	> 0.05

At T_2, 30 femoral heads (20 patients) were clinically evaluated. Compared with T_1, it showed statistically significant pain reduction results with $p < 0.01$. The improvement in mobility and ability to walk was not statistically significant.

Table 4: Evaluation of the results of pain relief, improvement of movement and walking ability before, and after treatment.

Characteristics \ Time point		T_0 (n, %)	T_2 (n, %)	p
Pain level according to VAS (n = 30 FHs)	Severe	19 (63.3%)	7 (23.3%)	
	Moderate	9 (30.0%)	7 (23.3%)	
	Mild	2 (6.7%)	12 (40.0%)	
	No pain	0 (0.0%)	4 (13.3%)	-
	Mean VAS score	7.03 ± 1.90	3.77 ± 2.64	
Hip ROM (degree) (n = 30FHs)	Flexion	87.17 ± 13.69	101.50 ± 14.69	
	Abduction	21.50 ± 5.89	28.50 ± 7.09	< 0.001
	External rotation	28.33 ± 4.01	34.00 ± 5.15	
	Internal rotation	30.33 ± 4.90	34.17 ± 4.93	
Ability to walk (n = 20 patients)	Very limited	2 (10.0%)	1 (5.0%)	
	Slight limitation	18 (90.0%)	15 (75.0%)	-
	Normal	0 (0.0%)	4 (20.0%)	
	Mean Merle D'Aubigné Score	4.05 ± 0.83	4.95 ± 0.76	< 0.001

The results of pain reduction, improvement of movement and walking ability were markedly improved in T_2 compared to T_0 with $p < 0.001$.

Table 5: Evaluation of changes in the image of lesions on magnetic resonance imaging of the femoral head at T_2.

Characteristics \ Time point			T_0 (n = 30)		T_2 (n = 30)		p
			n	%	n	%	
Bone marrow edema	No		10	33.3	18	60.0	< 0.05
	Yes		20	66.7	12	40.0	
Hip effusion	No		13	43.3	13	43.3	-
	Yes	Grace 1	5	16.7	13	43.3	
		Grace 2	12	40.0	3	10.0	
		Grace 3	0	0.0	1	3.3	
% area of involvement	< 15%		3	10.0	3	10.0	> 0.05
	15 - 30%		7	23.3	5	16.7	
	> 30%		20	66.7	22	73.3	
% length of crescent	No		11	36.7	11	36.7	> 0.05
	Yes	< 15%	5	16.7	3	10.0	
		15 - 30%	5	16.7	6	20.0	
		> 30%	9	30.0	10	33.3	
% surface collapse	No		12	40.0	12	40.0	-
	Yes	< 15%	17	56.7	11	36.7	
		15 - 30%	0	0.0	6	20.0	
		> 30%	1	3.3	1	3.3	

After 5 months of treatment, the rate of bone marrow edema decreased after treatment was statistically significant with $p < 0.05$. The proportion of hip joints with grade 2 effusion decreased, the rate of grade 1 effusion increased, and there was one hip joint with grade 3 effusion. The percentage of the femoral head with lesion area < 15%, no subchondral fracture unchanged after PRP treatment. There were 06 femoral heads (20.0%) that increased the area of femoral collapse after treatment.

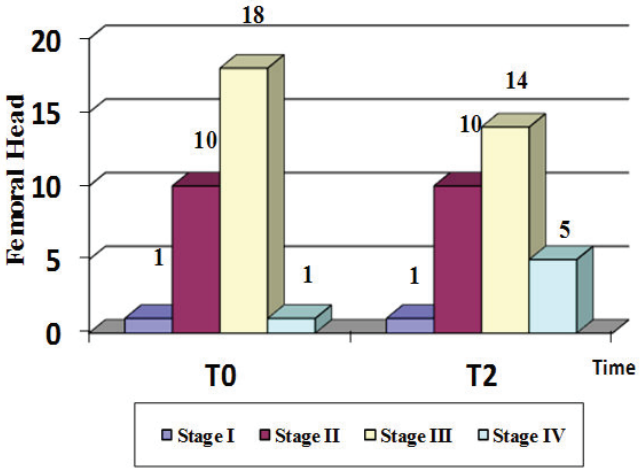

Chart 1: Change of lesion stage of FH after 5 months of treatment.

After 5 months of treatment, four FHs from ARCO stage III progressed to ARCO stage IV, and the change of lesion stage of FH was statistically significant with $p < 0.05$.

DISCUSSION

Our study had 30 patients with an average age of 53.83 (30 - 73 years old), including 21 male patients (70.0%) and 9 female patients (30.0%). The number of FHs interventions was 47, which were classified 1 as stage I, 14 as stage II, 26 as stage III and 5 as stage IV. Patients with stage IV ANFH wanted to delay hip replacement. In 2020, a female patient with ARCO stage IV ANFH due to Glucocorticoid received 5 consecutive ultrasound-guided injections of platelet-rich plasma. At the 9-month follow-up, clinical and radiological re-evaluations showed a marked improvement. This case highlighted the therapeutic potential of platelet-rich plasma injections for the late-stage ANFH [6].

As a pathological process, osteonecrosis of the FH is characterized by the avascularity of the FH, cellular necrosis, microfracture, and the collapse of the articular surface. PRP containing concentrations of platelets greater than the baseline plays an important role in tissue repair, regeneration, and the differentiation of mesenchymal stem cells. PRP treats ANFH mainly through three mechanisms: inducing angiogenesis and osteogenesis to accelerate bone healing, inhibiting inflammatory reactions in necrotic lesions, and preventing apoptosis induced by glucocorticoids [7]. Studies use repeated PRP as a treatment with a longer duration of

action than a single injection. However, the obvious disadvantages of injection are the pain caused and the potential infection risk; therefore, the number of injections should be kept to a minimum [8]. Therefore, we chose a regimen of 2 injections of PRP one month apart for the study subjects. To complete the bone regeneration process it took 3 - 4 months, followed by a long rest period before starting the next period of the bone renewal cycle. Though the time to re-evaluate the magnetic resonance after 5 months of treatment was appropriate.

At T_1 (one month after the first injection), 47 FHs (30 patients) were clinically evaluated according to the following criteria: Pain relief, improvement of movement, and walking ability. Among them, 40 FHs were injected with the 2nd injection. At T_2, clinical evaluation and MRI were performed on 20 patients (30 FHs).

Evaluating the pain relief results of this treatment according to the VAS in 47 FHs at T_1 was 5.38 ± 2.03, decreased in comparison to T_0 (7.28 ± 1.74), statistically significant with $p < 0.001$. At the time of T_2, the mean VAS score was 3.77 ± 2.64, lower than the VAS score of the corresponding 30 FHs at T_1 (4.67 ± 1.89) with $p < 0.01$. The number of painful hip joints at T_0 was 33/47 (70.2%). By T_2, the number of hip joints with severe pain decreased to 7/30 (23.3%), and 4/30 (13.3%) had no pain. The study by Shuo Luan, et al. on 30 FHs (30 patients) stages I, II, III ARCO injected with 4 doses of PRP at 0, 3, 6, 9 months also showed VAS scores decreased from 6.13 to 3.4 after 1 month of the first injection ($p < 0.001$) and 3.00 after 6 months of the first injection [9]. Thus, the analgesic effect of PRP markedly improved after 1 month of injection and had a sustained effect.

Comparing the average value of the VAS score, hip ROM between the study time points showed that there was a marked improvement in T_1 and T_2 compared to T_0 ($p <0.001$), but the difference was not statistically significant at T_2 compared to T_1. According to Ibrahim's study, the patient improved hip ROM at her 1-month follow-up visit after the PRP injection (hip extension and abduction increased from 15° to 35°.

Our results showed that before the first injection of PRP (T_0), all patients had difficulty walking, of which 10/30 patients had very limited mobility and had to use crutches or a walking stick. At the time points of the final follow-up (T_2), only 1/20 had very limited

mobility, and 4/20 patients had normal mobility. Assessing the patient's walking ability according to the Merle D'Aubigné scale, we found a statistically significant improvement, with $p < 0.001$ at T_2 and T_1 compared to T_0.

Assessing the change in the image of lesions on MRI of the FHs after 5 months of treatment, there were 8 FHs (26.7%) without the image of bone marrow edema. The reduction after treatment was statistically significant, with $p < 0.05$. The proportion of hip joints with grade 2 effusion decreased from 12/30 to 3/30, of which there were 8 hip joints with reduced effusion (grade 1), and 1 hip with increased effusion (grade 3). The percentage of FHs with lesion area < 15% did not change after PRP treatment, 02 FHs (6.7%) increased the area involvement from 15 - 30% to > 30%. The rate of FHs without subchondral fracture after 6 months of PRP treatment remained unchanged, 2 FHs with subchondral fractures < 15% increased to 15 - 30% and 1 FH had subchondral fractures from 15 - 30% increase to >30% of FH area. Considering the progress of FH collapse after PRP treatment, we found that only 06 FHs (20.0%) increased surface collapse of FH from < 15% to 15 - 30% after treatment.

Regarding the change of lesion stage of 30 FH s with MRI results after 5 months of PRP treatment, we found 11/11 FHs early stage necrosis (1 as stage I and 10 as stage II) kept the necrotic stage. 4/18 FHs stage III progressed to stage IV. The progression stage of FH necrosis was statistically significant with $p < 0.05$. Shuo Luan's study showed that 1 FH moved from ARCO stage II to I, and 1 FH stage III progressed to stage IV after 12 months [9]. The study by Shuo Luan showed that a longer study period was needed to evaluate the change stage of FH necrosis.

PRP contains growth factors that stimulate regeneration and are anti-inflammatory and analgesic; thus, it reduces inflammation and pain. According to our study, the rate of bone marrow edema decreased after treatment which also reduced pain symptoms. Hanataka reported that the prevalence of bone marrow edema was 87.0% in the symptomatic group and 0% in the asymptomatic group ($p < 0.0001$) [10]. Bone marrow edema of the FH was strongly associated with hip pain. Pain improvement usually parallels the resolution of edema. As a result, the patient's hip range of motion and walking ability was improved. This study showed that FHs early stage necrosis kept the necrotic stage, and

4/18 FHs stage III progressed to stage IV. However, similar to the results of other studies, PRP was not shown to be an effective method for treating advanced stage ANFH [7].

CONCLUSION

The results of medical treatment combined with autologous platelet-rich plasma injection for patients with ANFH have markedly improved analgesia and motor function after 5 months. Further studies with longer follow-ups are needed in the future to standardize treatment regimens for ANFH with PRP.

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