Early assessment the effect of intraarticular autosomal platelet-rich plasma injection in the primary knee osteoarthritis treatment

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Abstract

Introduction/Background: Osteoarthritis is a degenerative joint disease that commonly occurs in the elderly population. Treatment goals include pain relief, improvement in knee function, improved quality of life and reduction in disability. Several studies describe the use of biological therapies such as autosomal platelet-rich plasma as effective and safe methods in the treatment of pain and joint dysfunction caused by knee osteoarthritis. **Objectives:** To evaluate the analgesic, mobility functional improvement efficacy, and safety of intraarticular autosomal platelet-rich plasma (PRP) injection in the primary knee osteoarthritis treatment. **Materials and Methods:** Prospective descriptive study of 38 knee joints of 31 patients was diagnosed with primary osteoarthritis according to the American College of Rheumatology (ACR) classification criteria and in Kellgen & Lawrence grade II, III. The patient was assessed about clinical features, subclinical features and the VAS score, Lequesne index at the initial of the study and 30 days later. **Results:** The VAS score at 30 days post-injection of PRP lower than the initial value with a statistically significant difference (40.55 ± 9.65 and 65.71 ± 10.06, respectively, with $p < 0.001$). The Lequesne index at 30 days post-injection of PRP lower than the initial value with a statistically significant difference (12.50 ± 2.64 and 16.74 ± 2.40, respectively, with $p < 0.001$). The improvement of VAS score and Lequesne index is better in the patient with Kellgren & Lawrence grade II than those with Kellgren & Lawrence grade III (27.24 ± 6.55 and 22.59 ± 5.95, respectively, with $p < 0.05$). The incidence of the observed complications was not reported in this study. **Conclusions:** The intraarticular PRP injection in the primary knee osteoarthritis treatment is a safe approaching and has a significant effect on pain relief and physical function improving after 30 days. The improvement of the VAS score and Lequesne index is greater in the patient with the early grade on Kellgren & Lawrence classification.

Keywords: *Knee osteoarthritis, intraarticular injection, autosomal platelet-rich plasma, PRP.*

1. INTRODUCTION/BACKGROUND

Osteoarthritis is a degenerative joint disease that commonly occurs in the elderly population. Treatment goals include pain relief, improvement in knee function, improved quality of life and disability reduction. However, no current drugs able to cease the osteoarthritis progressive or converse the already lesion. Most of the approach treatments concentrate on modest invasive that could apply in the early stage of the osteoarthritis process when degenerative structure changes could be stopped and delayed.

PRP is a product derived from autologous blood with a high concentration of activated platelets in a small plasma volume. It can release a host of mediators and growth factors such as insulin growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular EGF (VEGF), transforming growth factor-β (TGF-β), and others that act during the initial phase of tissue healing and regeneration. In vitro, PRP has been shown to have large and complex biological activities, including cellular proliferation, anti-apoptotic activity, cartilage regeneration, collagen synthesis, angiogenesis, and increased vascular permeability [4]. PRP has been widely used in the clinical setting for tissue regeneration and repair. Recently, especially in the field of sports medicine and orthopedics, PRP has demonstrated regenerative ability to repair injured tissues, including tendons, ligaments, and cartilage, all of which have a low intrinsic healing potential [8]. Several studies described the use of biological therapies such as autosomal platelet-rich plasma as an effective and safe method in the treatment of pain and joint dysfunction caused by knee osteoarthritis [7].

The purpose of this study was to evaluate the analgesic, mobility functional improvement efficacy, and safety of intraarticular autosomal platelet-rich

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plasma injection in the primary knee osteoarthritis treatment.

2. Materials and Methods

2.1. Patient Selection: A total of 31 patients at The General and Endocrinology Department of Hue University of Medicine and Pharmacy Hospital from September 2019 to December 2020 with 38 knee joints was diagnosed with primary knee osteoarthritis according to the American College of Rheumatology classification criteria [1].

Knee: Clinical and Radiographic
1. Knee pain for most days of the prior month
2. Osteophytes at joint margins
3. Synovial fluid typical of osteoarthritis
4. Age ≥ 40 years old
5. Morning stiffness lasting ≤ 30 minutes
6. Crepitus with active joint motion
Diagnosis requires 1+2, or 1+3+5+6, or 1+4+5+6

At grade II and grade III on radiograph according to Kellgren & Lawrence classification:

+ Grade I: Minute osteophyte: doubtful significance

+ Grade II: Definite osteophyte: normal joint space.

+ Grade III: Moderate joint space reduction.

+ Grade IV: Joint space greatly reduce: subchondral sclerosis

- Suitable for PRP injection (Hb values > 11 g/dl and platelet values > 150000/mm^3).

Exclude criteria:

- Patients who disagree with participate in the study or missed re-evaluated at the day of 30

- Patients use other drugs which have an effect on pain relief or osteoarthritis management during the follow-up time..

- Patients have coagulation disorders or on anticoagulant therapy

- Patients with severe chronic disease (heart failure, renal failure, cirrhosis, tuberculosis, uncontrolled diabetes or hypertension,...)

- Patients who have skin infection at injection knee or other severe infectious states.

2.2. Study design: We performed a prospective descriptive study with 30 days long follow-up after the initial PRP injection. The efficacy of treatment was measured through the VAS score and Lequesne index.

- Pre-evaluation participants

+ All patients who agreed to take part in the study were evaluated in clinical aspects and medical history.

+ In the case of a patient who presented with joint effusion in the study knee, the patient would be given a short-term NSAID to reduce the joint fluid before PRP injection or be done simultaneously arthrocentesis and PRP injection process.

+ In the case of a patient younger than 65 years old and on oral Diacerein, this would be given a stable dose at least four weeks before the study process.

- Patient who suitable for study would be accessed about clinical features (VAS score, Lequesne index), subclinical features (radiography).

- Then, intraarticular PRP injection was done on the initial day of the study (D0 – day 0).

+ Use a 50ml – syringe with already anticoagulant to collect a total of 30 ml venous blood per knee joint from the patients.

+ All the mixture of venous blood and anticoagulant was pumped to PRP kit (TriCellPRP).

+ First centrifugal: PRP kit was centrifuged at a rate of 3300 rpm for 3 minutes to fix and separate the erythrocyte compartment.

+ Second centrifugal: PRP kit was centrifuged at a rate of 3200 rpm for 5 minutes to fix and separate the platelet-rich compartment.

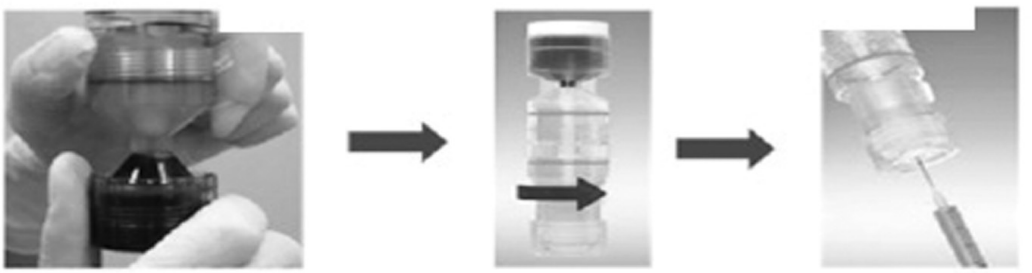
+ Platelet-rich plasm was drawn from the PRP kit by 5ml-syringe before it was injected into the patient's knee joint.

+ This type of PRP kit did not require to use of an onal filter or activation agent.

After intra-articular injection, we don't use any more drugs and observe the adverse event during 24 hours at the hospital before sending the patient back home and follow up through mobile phone if any events would have occurred.

– Patient would be reaccessed on the 30th day (D30) after intra-articular PRP injection about the efficacy through VAS score and Lequesne index, and the adverse events.

Step 1 Step 2



Step 3 Step 4 Step 5

3. RESULTS

3.1. The patient's characteristics

Table 1. Demographic Data Before Treatment

		n	%	Mean ± SD
Age (years)	40 – 50	02	6.45	- 61.16 ± 7.81
	51 – 60	15	48.39	
	61 – 70	11	35.48	
	>70	03	9.68	
Sex	Male	10	32.26	
	Female	21	67.74	
BMI (kg/m^2)	<23	13	41.94	- 23.68 ± 3.08
	≥23	18	58.06	
K-L classification	Grade II	21	55.26	
	Grade III	17	44.74	
VAS pain score at day 0 (0-100)	<70	20	52.63	65.71 ± 10.06
	≥70	18	47.37	
Knee joint	Right knee	16	42.11	
	Left knee	22	57.89	

Of a total 31 patients with 38 knee joints fitting the inclusion criteria were followed in the PRP intraarticular injection treatment. The average age was 61.16 years (SD = 7.81, min = 47, max = 83), with 85 percent in the range 51 – 70 years old. Female was majority approximately two-thirds patients. The mean BMI was 23.68 kg/m^2 (SD = 3.08, min = 16.65, max = 29.30). Overweight and obesity were greater and account for 58.06 percent. The majority radiographic lesion is grade II in Kellgren & Lawrence classification with approximately 52.26 percent. Twenty patients had a VAS score of less than 70mm with the proportion was 52.63 percent. The left knee joint was more than the right one (22 and 16, respectively).

3.2. The analgesic efficacy and mobility functional improvement efficacy of intraarticular PRP injection

Table 2. VAS score and Lequesne index at the 30th day

	n	D0 (± SD)	D30 (± SD)	$P_{pre - post}$
VAS	38	65.71 ± 10.06	40.55 ± 9.65	<0.001
Lequesne	38	16.74 ± 2.40	12.50 ± 2.64	<0.001

The VAS score at 30 days post-injection of PRP was lower than the initial value with a statistically significant difference (40.55 ± 9.65 and 65.71 ± 10.06, respectively, p <0.001). The Lequesne index at 30 days post-injection of PRP was lower than the initial value with a statistically significant difference (12.50 ± 2.64 and 16.74 ± 2.40, respectively, p <0.001).

Table 3. The relationship between the analgesic efficacy through VAS score and relative factors

Relative factors		n	ΔVAS	p
Age	≤ 65	26	25.92 ± 6.09	p >0.05
	> 65	12	23.50 ± 7.69	
Sex	Male	12	23.17 ± 9.28	p > 0.05
	Female	26	26.08 ± 4.94	
Knee joint	Right	16	25.75 ± 5.76	p > 0.05
	Left	22	24.73 ± 7.30	
BMI (kg/m^2)	≥23	23	25.78 ± 7.89	p > 0.05
	<23	15	24.20 ± 4.11	
K-L classification	Grade III	17	22.59 ± 5.95	p < 0.05
	Grade II	21	27.24 ± 6.55	
VAS score at the initiation (D0)	≥70	18	26.83 ± 7.29	p > 0.05
	<70	20	23.65 ± 5.74	

Table 4. The relationship between the mobility improvement efficacy through Lequesne index and relative factors

Relative factors		n	ΔLequesne	p
Age	≤ 65	26	4.31 ± 1.74	p > 0.05
	> 65	12	4.08 ± 1.24	
Sex	Male	12	3.83 ± 2.13	p > 0.05
	Female	26	4.42 ± 1.27	
Knee Joint	Right	16	4.19 ± 1.28	p > 0.05
	Left	22	4.27 ± 1.80	
BMI ($kg/m^{2)}$	≥ 23	23	4.04 ± 1.69	p > 0.05
	< 23	15	4.53 ± 1.41	
K-L classification	Grade III	17	3.35 ± 1.41	p < 0.05
	Grade II	21	4.95 ± 1.36	
VAS score at the initiation (D0)	≥ 70	18	3.94 ± 1.89	p > 0.05
	< 70	20	4.50 ± 1.24	

Overall, the improvement of VAS score and Lequesne index were better in the patient with Kellgren & Lawrence grade II than those with Kellgren & Lawrence grade III (VAS score: 27.24 ± 6.55 and 22.59 ± 5.95, respectively, with p<0.05). However, there is no relationship between the improvement of VAS score or Lequesne index and other factors, including age group, sex, knee joint site, BMI or the initial VAS score.

3.3. The safety of intraarticular autosomal platelet-rich plasma injection method

Table 5. The incident of adverse events

Adverse event	N	%
Post-injection flare	0	0
Hemorrhage at the injection site	0	0
Infection	0	0
Local adverse reactions (skin atrophy or hypopigmentation)	0	0
Others (vagal reaction, hypersensitivity)	0	0
Total	0	0

During follow-up of the 38 knee joint was injected PRP, the observed complications including post-injection flare, hemorrhage and infection at the injection site,... was not reported.

4. DISCUSSION

Of a total of 38 intraarticular PRP injected knee joints, after 30 days of follow-up, the results documented that PRP injection had an effect on pain relief through VAS score and on recovery mobility function through Lequesne index. Those results are similar to article of Dai W.L., a meta-analysis on 10 randomized controlled trials with a total of 1069 patients done PRP injection for the treatment knee of osteoarthritis. Their analysis showed that PRP had effects on pain relief (WOMAC score) and functional improvement (WOMAC function score, WOMAC total score, IKDC score, Lequesne score) at 6 months and 12 months after postinjection. However, PRP had more benefits than HA and saline at 12 months though it was similar to HA at 6 months [5]. Meheux C.J. et al, in a systematic review of 6 articles from PubMed, Cochrane Central Register of Controlled Trials, SCOPUS and Sport Discus, also showed that PRP injection resulted in significant clinical improvement up to 12 months post-injection and significantly better than HA at 3 to 12 months post-injection in clinical outcomes and WOMAC score [9].

Shen L. et al in a systematic and meta-analysis of 14 randomized controlled trials comprising 1423 participants included found that in comparation with controls, intra-articular PRP injections significantly pain relief through reduced WOMAC pain subscores at 3, 6, and 12 months follow-up (with $p < 0.02$; 0.004; <0.001, respectively) and also significantly improved WOMAX physical function subscores at 3, 6, 12 months (with $p = 0.002$; 0.01; <0.001, respectively). PRP had also significantly improved total WOMAC scores at 3, 6 and 12 months (all $p < 0.001$); nonetheless, PRP did not significantly increased the risk of post-injection adverse events (RR, 1.40 [95% CI, 0.80 to 2.45], I 2 = 59%, p = 0.24) [11].

Rodriguez-Garcia S.C. et al have done an overview of 29 final systematic reviews included and updated in 2020 had reported that, overall, better performance for pain and function seen in knee osteoarthritis with large effects in comparing to placebo or hyaluronic acid. This trend was not present in hip osteoarthritis, with only a few randomized controlled trials showing a modest effect on pain. One consistent observation between studies was that the PRP effect lasted longer than its comparators (commonly, hyaluronic acid). In Anitua E.'s article, it has been reported that they played additional roles, including promotion of tissue repair and regeneration, vascular remodeling and mediators in the inflammatory and immune responses. Platelets release a pool of biologically active proteins and other substances that enable them to influence a range of processes promoting the recruitment, growth and morphogenesis of cells [2].

In relationship to patient factors, the presented results reported that the analgesic efficacy and functional improvement in patients with radiograph grade II in Kellgren & Lawrence greater than those in grade III. This association was reported by Filardo G. et al when they did a randomized controlled trial in 55 patients treated with HA and 54 patients treated with PRP and evaluated at 12 months of follow-up. Authors suggested that PRP injection offered a significant clinical improvement up to one year of follow-up and more promising results shown for its use in low-grade degeneration but they still have to be confirmed. Whereas PRP and HA could provide the same outcome in knees with Kellgren Lawrence III level, less degenerated joints showed a different trend, with a tendency toward better results in the PRP group at 6 and 12 months of follow-up, albeit without reaching statistical significance (p=0.08 and

p=0.07, respectively) [6].

In 2015, Kanchanatawan W. et al did a systematic review and meta-regression to compare outcomes of the PRP injection to HA or placebo in the 566 studies identified from Medline and Scopus. They have reported that, about short-term outcomes (≤1 year), PRP injection has improved functional outcomes (WOMAC total scores, IKDC score, and EQ-VAS) in comparison to HA and placebo while it had no statistically significant difference in adverse events in comparison to HA and placebo. This study suggested that PRP injection was more efficacious than HA injection and placebo in reducing symptoms and improving function and quality of life. It has the potential to be the treatment of choice in patients with mild-to-moderate OA of the knee who have not responded to conventional treatment [7]. The presented evidence implies that when the treatment applies in the early stage of osteoarthritis in which the cartilage was just minimal damaged by the degenerative progression would have more benefit on treatment efficacy. However, this hypothesis needs to be confirmed by more researches in the future.

In our study, of all the 38 knee joints injected with PRP, we did not recognize any adverse events, especially no severe event and this agreed with previous authors. In 2014, in a systematic review and network meta-analysis of 137 studies comprising 33,243 participants, Bannuru R.R. et al represented that the commonly reported adverse events were transient local reactions with pain and swollen in a few days while the incident is similar between the intraarticular injection therapies [3]. Dai W.L et al also found that PRP did not increase the risk of adverse events compared with HA and saline [5].

In 2017, Nguyen C. and Rannou F. carried out a critical narrative review on the safety of intra-articular injections treatment for knee osteoarthritis. In this review, the current body of evidence suggested that the safety profile of intraarticular PRP was comparable to the one of intraarticular hyaluronic acid. Self-limited post-injection pain and swelling were the most frequently reported adverse events. As for other intraarticular therapies, safety outcomes were inconsistently reported [4].

Newly, Rodriguez-Garcia S.C. et al were also aware that safety is the best studied in large long-term observational studies. They retrieved information regarding adverse events from the systematic reviews of random controlled trials. Several injection therapies comprise hyaluronic, glucocorticoid and PRP,.. have been included as the comparator and found that the frequency of any adverse event remarkably was low and no increased risk or only for local reactions [10].

5. CONCLUSION

The intraarticular PRP injection in the treatment of primary knee osteoarthritis is a safe approach with a significant effect on pain relief and mobility function improving after 30 days post-injection. The improvement of the VAS score and Lequesne index is better in the patients who presented with the early grade on Kellgren & Lawrence classification. However, further studies should be performed to confirm this advantage result. The efficacy of intraarticular PRP injection does not see the relation with age, sex, knee joint site, BMI, or the initial VAS score.

6. PROPOSE

At examination room/inpatient room:
- Assess the indication (knee osteoarthritis grade II, III).
- Exclude the contraindication (Hb values ≤ 11 g/dl and platelet values ≤ 150000/mm^3; contraindication for intraarticular injection).

⇩

At PRP room/ procedure room:
- Take 30ml venous blood from the patient with anticoagulation. - Then, centrifugal and separate into 5ml finally product from the venous blood. - Injection 5ml PRP product into indicated knee joint.

⇩

At inpatient room:
- Patient will be followed for adverse events after intraarticular injection within 24 hours before discharge.

As our study, the intra-articular PRP injection could be order to knee osteoarthritis patient in the grade II, III on Kellgren & Lawrence classification.

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