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Platelet-rich autologous plasma for the treatment of patients with grade II osteoarthritis of the knee

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Introduction There have not been highly effective and equally safe tools available to relieve pain and improve joint function in patients suffering from osteoarthritis. **Purpose** Explore the efficacy of intra-articular application of autologous platelet-rich plasma (PRP) in the treatment of patients affected by grade 2 osteoarthritis of the knee. **Material and methods** The study was designed as a single-arm prospective randomized trial. A total of 60 patients with grade 2 osteoarthritis according to the J. Kellgren and J. Lawrence grading scale (1957) were enrolled in the study. Patients were divided into two clinical groups, with 30 subjects in each group. Index clinical group was treated using three 2 mL intra-articular applications of PRP performed once over a 3-week period. Control group was given three intra-articular injections of 2 mL hyaluronic acid (HA) applied once a week. Outcome measures included verbal rating scale of treatment effectiveness (VRSte), 100-point pain visual analogue scale (VAS), and Lequesne scale taken at 1-, 3-, 6- month follow-up. **Results** Measurement with VAS showed decrease in pain from 50.5 ± 5.38 to 9.8 ± 3.39 ($p < 0.05$) in index group one month after intra-articular applications of PRP. Analgetic effect persisted at a 6-month follow-up without statistically considerable changes. Control group showed decrease in pain from 46.8 ± 6.49 to 19.73 ± 5.84 ($p < 0.05$) scores one month after intra-articular applications of HA and decline in scores of 27.76 ± 7.72 ($p < 0.05$) at 6–month follow-up. Index group demonstrated considerable reduction in Lequesne score from 10.88 ± 1.63 to 4.2 ± 1.23 ($p < 0.05$) one month after treatment that persisted at 6-month follow-up. Control group also showed reduction in Lequesne score from 9.9 ± 1.6 to 4.7 ± 0.66 ($p < 0.05$) at one-month follow-up that remained nearly the same 6 months after treatment. **Conclusion** Our findings suggest that intra-articular application of PRP in the treatment of patients with grade 2 osteoarthritis of the knee can provide pain control and functional improvement to a greater extent as compared to HA injections throughout 6-month follow-up.

Keywords: osteoarthritis of the knee joint, platelet-rich plasma, hyaluronic acid

INTRODUCTION

Osteoarthritis (OA) describes a heterogenic group of disorders of various aetiology with similar biological, morphological, clinical manifestations and outcomes that are associated with involved components of joints including cartilage, subchondral bone, synovium, ligaments, capsule and periarticular muscles [1]. Osteoarthritis is considered to be one of the most common musculoskeletal disorders. According to World Health Organization, an estimated 4 % of world's population suffers from OA and the disease leads to disability in 10 % of the cases in older adults, in particular [2].

Patients with deforming arthritis of major joints are a special group in clinical practice of orthopaedic and trauma surgeons since the existing techniques of treatment often fail to provide positive outcomes. There have not been highly effective and equally safe tools available to relieve pain and improve joint function in osteoarthritis [3].

Among several successful approaches in treatment of early OA intra-articular injections of hyaluronic acid (HA) were found to be effective in pain reduction and functional improvement for the period of one year and over [4].

The possibility to control biological potential of the patient's body and utilize it for treatment was reported as an encouraging application in some publications on platelet-rich plasma (PRP). Due to numerous growth factors contained in platelet alpha-granules that are acutely or slowly released into the surrounding environment PRP acts to inhibit inflammation, help regeneration and repair tissues [5]. Therefore, recent studies have been focused on therapeutic effect of intra-articular application of PRP for patients with OA of the knee, in particular. The findings remain controversial as to symptom- and disease-modifying action of PRP, association between the results obtained, the dynamics, and phase of the disease [6].

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The objective of the present study was to explore the efficacy of intra-articular application of autologous platelet-rich plasma (PRP) in the treatment of patients affected by grade 2 osteoarthritis of the knee.

MATERIAL AND METHODS

The study was designed as a single-arm prospective randomized study. A total of 60 working-age patients with grade 2 osteoarthritis of the knee according to the J. Kellgren and J. Lawrence grading scale (1957) and unilateral (15 %) and bilateral involvement (85 %) were enrolled in the study. Patients were subdivided into two clinical groups, with 30 subjects in each group.

The research was in compliance with ethical standards of the Declaration of Helsinki of 1975, amendments of 2008, and the clinical study "Platelet-rich autologous plasma for the treatment of patients with grade 2 osteoarthritis of the knee" was approved by Ethical Review Board of FSEI HPE "Volgograd State Medical University" RF Ministry of Health in 2013.

The disease was diagnosed based on clinical criteria, laboratory and radiological assessments according to Federal clinical practice guidelines for diagnosis and treatment of osteoarthritis.

Decrease in the knee joint space by 50 % at most (not more than 4 mm) in stress orthopositioned radiograph was a major radiological sign.

Patients with radiographic evidence of Kellgren-Lawrence grade 2 knee OA, expressed pain (60 to 80 VAS points) and cases of inadequate efficacy of the previous treatment met the inclusion criteria. Patients aged less than 30 years who had blood disorders, hepatitis B virus, hepatitis C virus, HIV, accompanying pathology of visceral organs at decompensation, neoplastic lesions, systemic disorders, those receiving anticoagulant therapy, having signs of acute inflammation of various localization were excluded from the study.

Thirty patients of the index group and thirty patients of the control group met inclusion criteria (**Table 1**).

The most average patient in the study was a female aged 47 ± 3.64 years with body mass index of 28.5 ± 0.92, suffering from primary bilateral grade 2 osteoarthritis of the knee during 2 ± 0.36 years, having an accompanying pathology of stage 1 hypertension and taking not more than 2 groups of antihypertensive drugs (ACE inhibitor, beta adrenergic receptor blocking agent), showing inadequate efficacy from the previous treatment with one of nonsteroidal anti-inflammatory agents and poor compliance with long-term treatment.

PRP was prepared and injected in the knee joint of a patient at a dressing room. First, 40 ml of whole blood was collected from the patient's median cubital vein with a syringe and poured into hermetically closed sterile translucent plastic container. Ten milliliter of 5 % sodium citrate solution was added at ratio of 1:4 and put in a RotoFix 32 centrifuge (Hettich, Germany) with appropriate counterweight and rotated at 1800 rpm for 10 minutes for the first time. Then 20 ml of supernatant were decanted and placed in another sterile container (**Fig. 1a**).

Following the second centrifugation at 3400 rpm for 10 minutes another 15 ml of supernatant were decanted and precipitated formed elements diluted in the remaining plasma (**Fig. 1b**). Plasma was collected from the bottom of container with a syringe and 0.1 ml of 10 % calcium chloride solution was added to activate platelets. 1.5 ml of PRP produced was required for platelet count that was $912 \pm 40 \times 10^{9/l}$.

With aseptic and antiseptic conditions of a dressing room intra-articular application of PRP was performed for the patients of index group employing a standard anteromedial/anterolateral approach. Three 2 mL intra-articular injections of PRP were applied once over a 3-week period. Control group was given three intra-articular injections of 2 mL HA applied once a week in a similar manner.

Table 1

Characteristics of clinical groups

Description	Index group	Control group
Number of patients	30	30
Gender	14♂, 16♀	10♂, 20♀
Age, years	49.3 ± 10.97	44.46 ± 8.87
Age of the disease, years	2.84 ± 0.89	2.5 ± 0.61
Body mass index, kg	29.13 ± 2.68	27.77±2.34
RBC	$(4.6 \pm 0.17) \times 10^{12}$/l	$(4.6 \pm 0.14) \times 10^{12}$/l
WBC	$(5.0 \pm 0.1) \times 10^{9}$/l	$(4.9 \pm 0.14) \times 10^{9}$/l
Platelet count	$(263.47 \pm 13.1) \times 10^{9}$/l	$(234.82 \pm 14.34) \times 10^{9}$/l
ESR	13.73 ± 1.2 mm/h	14.17 ± 1.4 mm/h
CRP	less than 5 mg/ml	less than 5 mg/ml
High blood pressure	12	14

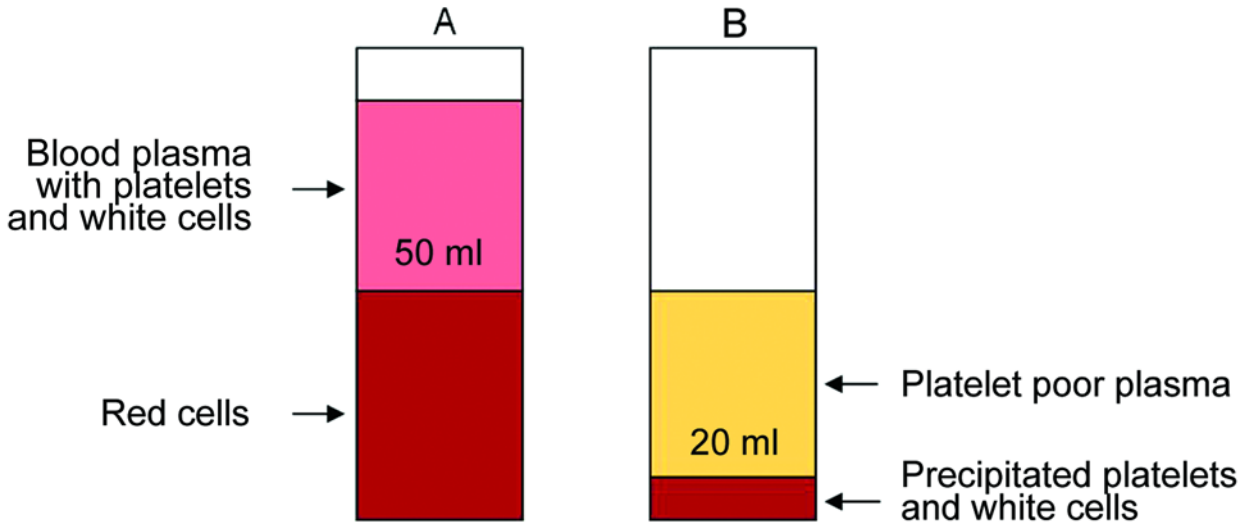

Fig. 1 Diagram of whole blood separation at the first (**a**) and the second (**b**) centrifugation

Outcome measures of both clinical groups included verbal rating scale of treatment effectiveness (VRSte), 100-point pain visual analogue scale (VAS), and Lequesne scale prior to PRP/HA applications taken at 1, 3, and 6 months following the course of intra-articular injections.

Excel Microsoft Office (Microsoft, U.S.A.) and STATISTICA 10.0 (Stat Soft Inc., U.S.A.) were used for basic statistical analysis of data with personal computer. Student's t-test was applied for normal value distribution, Mann-Whitney for nonparametric quantitative variables, Wilcoxon test for dependent variables, and χ^2 and Fisher exact tests, for quantitative data. $P < 0.05$ was considered as statistically significant.

RESULTS

The mean platelet count in plasma obtained in our study was $912 \pm 40 \times 10^{9/l}$ that corresponded to criteria of PRP [4].

Two clinical groups were comparable by representation, major clinical, morphological parameters, initial VAS and Lequesne values ($p > 0,05$), and varied by technique used to treat OA of the knee, either by intra-articular injections of PRP or HA.

Complete course of treatment with evaluation of the outcomes at the end point of 6 months was performed for 30 (100 %) patients of index group and 30 (100 %) patients of control group.

Application of PRP injection was evaluated as poor in 3.3 % of the cases, fair in 23.3 % and good in 73.3 % of the patients at one-month follow-up using VRSte. Three-month follow-up exhibited some decline regarding initial subjective rating of treatment effectiveness followed by gradual deterioration at 6-month follow-up with 13.3 % poor results, 33.3 % fair outcomes, and 50 % good results (**Table 2**).

The control group that had intra-articular HA injections showed similar dynamics in the outcomes. At one-month follow-up patients reported 3.3 % poor results, 46.7 % fair results, and 50 % good outcomes. The rating had no substantial changes at 3-month follow-up but worsened due to greater redistribution of results in HA group at 6-month follow-up. Poor results were shown to increase to 13.3 %, fair results to 50 %, against decrease in good results down to 30 % (**Table 2**).

The pain VAS showed considerable improvement in index group from initial 50.5 ± 5.38 to 9.8 ± 3.39 scores ($p < 0.05$) at one-month follow-up. Positive dynamics persisted at 3-month follow-up but worsened at 6-month follow-up returning to one-month scores without statistically significant differences with the latter (**Table 3**).

Less improvement in the pain VAS was observed in patients of control group following HA intra-articular application. VAS scores showed positive dynamics decreasing from 46.8 ± 6.49 to 19.73 ± 5.84 ($p < 0.05$) at one-month but exhibited no changes at 3-month follow-up and worsened to 27.76 ± 7.72 at 6-month follow-up ($p < 0.05$) (**Table 3**).

Table 2

Results of treatment in index and control groups using VRSte (%)

Result of treatment	Ineffective		Poor		Fair		Good		Excellent	
Clinical group	HA	PRP	HA	PRP	HA	PRP	HA	PRP	PRP	HA
Prior to treatment	–	–	–	–	–	–	–	–	–	–
1-month follow-up	–	–	3.3	3.3	46.7	23.3*	50	73.3*	–	–
3-month follow-up	4.4	3.4	6.6	10	40	26.6	50	60	–	–
6-month follow-up	6.7	3.4	13.3	13.3	50	33.3	30	50	–	–

* – statistically significant differences with control group ($p < 0.05$)

Table 3

The pain VAS in groups 1 and 2

Clinical groups	Prior to treatment	1-month follow-up	3-month follow-up	6-month follow-up
Index group (PRP)	50.5±5.38	9.8±3.39*	12.8±6.66**	10.1±3.25**
Control group (HA)	46.8±6.49	19.73±5.84*	20.43±4.99*	27.76±7.72*

* – statistically significant differences with values measured before treatment ($p < 0.05$); ** – statistically significant differences between groups 1 and 2 ($p < 0.05$)

No pain at all or low pain intensity in patients of both clinical groups according to VAS scale resulted in functional performance of the knee measured on Lequesne scale. Furthermore, changes in Lequesne index indicated to dynamics in both VAS and VRSte scores.

A nearly threefold decrease from 10.88 ± 1.63 to 3.7 ± 0.45 points ($p < 0.05$) was observed with Lequesne index in patients of PRP group at one-month and a slight increase noted at 3- and 6-month follow-up without statistically significant differences (**Table 4**).

A twofold decrease in Lequesne index was observed in control group at one-month follow-up. Decrease in the scores from 9.9 ± 1.6 to 4.7 ± 0.66 ($p < 0.05$) persisted at 3-month follow-up and Lequesne scores insignificantly increased up to 5.11 ± 1.15 at 6-month follow-up.

One complication developed during PRP and HA treatment. Nine PRP patients and seven HA patients were concerned about a slight increase in the knee pain after the first injection that was resolved during the next several days without specific treatment and was not seen with subsequent applications. No other local complications like periarticular soft tissue swelling, synovitis, inflammation were observed in the groups. No association was found between PRP and HA treatment and comorbidity of hypertension.

Table 4

Treatment results in groups 1 and 2 evaluated with Lequesne scale

Clinical groups	Prior to treatment	1-month follow-up	3-month follow-up	6-month follow-up
Index group (PRP)	10.88±1.63	3.7±0.45**	4.9±1.62*	4.17±0.84*
Control group (HA)	9.9±1.6	4.7±0.66*	4.66±1.3*	5.11±1.15*

* – statistically significant differences with values measured before treatment ($p < 0.05$); ** – statistically significant differences between groups 1 and 2 ($p < 0.05$)

DISCUSSION

Among the challenging problems arising during treatment of patients with knee OA, decrease in pain and arrest of synovitis are of paramount importance. The known groups of medications (nonsteroidal anti-inflammatory drugs and corticosteroids) cannot always provide the solution for the above symptoms [7]. The long-term use of analgetic and anti-inflammatory drugs is associated with adverse effects on a number of vital organ systems. Of paramount importance is the recognition of co-morbid conditions and concomitant drugs that may increase the risk of NSAIDs in particular patients [8].

Analgetic and anti-inflammatory drugs used for intra-articular injections are limited to anesthetic, hyalu-

ronic acid and corticosteroids. The latter are most effective for the arrest of inflammatory process and pain relief but can be applied at a frequency of one intra-articular injection per 4 months. There is also a risk of rapid progression of the condition, aseptic necrosis and infection [9].

More than 20 years of experience have shown that HA injections have beneficial effect due to hyaluranons that provide improvements in synovial fluid mechanical properties like elasticity and viscosity for low friction of the articular cartilage at ambulation. Pharmokinetic properties of hyaluranon substances are not limited by mechanical role only. At physical activity, hyaluranons migrate to the lymphatic system of the joint capsule, bloodstream, and finally get absorbed in the liver with degradation to water and carbon dioxide. Clinical trials showed no correlation between the duration of hyaluranons' therapeutic effect and the mechanical role since positive effect appeared to persist throughout several months of intra-articular applications, although the half-life of hyaluranons in the joint is several days/weeks. Another hypothetic mechanism of action involves receptors to inhibit mediators of inflammation and phagocyte function, stimulate synthesis of the cartilage and suppress its degradation. Hyaluronic concentration is considered to be influenced by synovial fibroblasts with homeostasis maintained by specific cell surface receptors [4, 10].

A number of randomized placebo-controlled trials that examined the effects of HA application reported improvements in the knee pain and function that persisted up to one year. However, anti-inflammatory and analgetic effects exerted slowly following 3 to 5 injections that entailed higher costs and less affordability with a need to look at a different option [9].

Our findings are mostly in line with the assumptions. VAS pain showed a 3-fold decline in intensity compared with baseline at one-month follow-up of HA course of treatment. VRSte scores worsened at 6-month follow-up with more patients rating their pain score as "poor" and "fair". Similar dynamics was observed in Lequesne index with a twofold decrease at one month and gradual insignificant regressive increase at 3-to-6-month follow-up.

Recent studies have been focused on therapeutic effect of intra-articular application of PRP for patients with OA of the knee, in particular. The findings remain controversial as to symptom- and disease-modifying action of PRP, association between the results obtained, the dynamics, and phase of the disease [6, 11].

According to many researchers, at baseline levels, platelets function as a natural reservoir for growth factors that are stored in their granules. Signaling molecules including TGF-β, FGF, PDGF, IGF-I, IGF-II, VEGF release upon activation and initiate and regulate universal biological processes in supporting tissues, the healing of inflammation, cell proliferation, restoring viscoelastic properties to the synovial fluid of degenerative joint. Interestingly, attempts to identify one or several growth factors that might play a key role failed and no high discrete activity could be seen [5, 12].

In addition to growth factors enhanced expression of IL-1RA cytokines induced beneficial effects on regulation of reparative processes with the concentration increased by 140 times in plasma [13].

Several studies report correlation between an extent of PRP anti-inflammatory effect and platelet count. The most noticeable clinical effect was observed with 4-to-6-fold increase in platelet count. Plasma appeared to show little or no activity to elicit anti-inflammatory and regenerative processes with less platelet count in PRP and if the count exceeded 1,000,000/μl [12].

Application of PRP yielded a better knee function and pain reduction in patients with early stages of OA. Some recent studies have shown to be noteworthy.

Filardo J. et al. (2011) reported pain reduction and improved quality of life with three intra-articular PRP injections in 91 patients (57 males and 37 females) aged 50 years who presented a chronic degenerative condition. The mean duration of clinical effect was 9 months, however, the results remained somewhat higher than the initial baseline at 12 months [6].

Prospective randomized study performed by Kon E. et al. in 2011 reported outcomes of 150 patients with knee osteoarthritis who received three intra-articular PRP applications within 3 weeks. There was significant improvement in the knee pain and function at 6-month follow-up in patients with early osteoarthritis [14].

Shikokova L.Yu. et al. in 2012 treated 83 female patients aged from 42 years to 70 years with PRP injections produced twice a week over the period of 3 weeks and followed them for 3 months. The authors concluded that positive dynamics in functional condition of the knee was evident in persons with early osteoarthritis at one-month follow-up only [15].

Cerza F. et al. conducted a randomized controlled study in 2012 and reported more encouraging results of 120 patients with osteoarthritis who received 4 PRP injections and showed no differences in efficacy with regard to the degree of joint damage. PRP applications

provided better pain responses as compared to hyaluronic acid injections [15].

A randomized controlled study published by Patel S. et al. in 2013 demonstrated no statistically significant differences in functional results of 78 patients with osteoarthritis who received one or two intra-articular PRP injections. However, both clinical groups showed better response than placebo group, with a tendency to decrease in the last assessment at 6 months [16].

Khoshbin A. et al. conducted a systematic review in 2013 that included 4 randomized and 2 non-randomized studies with 577 patients divided into 2 clinical groups. PRP injections showed much more improvement as compared to HA or 0.9 % NaCl intra-articular applications used for patients older than 55 years with mild to moderate knee OA at 6 months [17].

In 2014 Mangone G. et al. examined 72 patients with primary knee osteoarthritis who were treated with three intra-articular PRP injections between 2010 and 2013. A good statistically significant pain response persisted for one year [18].

A non-placebo-controlled randomized clinical trial performed by Raeissadat S.A. et al. in 2015 involving 160 patients affected by knee OA suggested that PRP injection was more efficacious than HA injection in reducing symptoms and improving quality of life at 12 months with no regard to a grade of OA [10].

Our findings showed a 5-fold decrease in VAS pain scores at one-month of intra-articular PRP applications and the regress was greater than that with hyaluronic acid injections. Positive dynamics persisted to 3 months, with a tendency to decrease in the last assessment at six months returning to initial baseline values of one month without statistically considerable differences with the latter.

VRSte scores were 20 % higher in patients of index (PRP) group than those in the control (HA) group at one month. Decrease in subjective assessments of initial results was observed at 3 and 6 months, however, a positive response sustained at a long-term follow-up was higher in index group than in control patients by 20 %.

No pain at all or low pain intensity according to VAS scale resulted in favorable functional performance of the knee dynamically measured on Lequesne scale with nearly threefold decrease at one month of treatment followed by a slight increase of Lequesne index at 3- and 6-month follow-up without statistically significant differences between the scores. More benefits in changing Lequesne index could be seen in PRP patients than that in HA group at both short- and long-term follow-ups.

No complications or adverse effects were observed during PRP treatment except for a slight increase in the knee pain in 9 patients that resolved during the next several days after the first injection without specific treatment. A similar effect was reported in other clinical trials [6].

No PRP-related irritating effects like periarticular soft tissue swelling, synovitis, inflammation were observed in index group. On the contrary, the above conditions had a tendency to regress, and an extent of intra-articular exudation was not considered a strict predictor of inefficient treatment at the very start of PRP applications as reported by L. Yu. Shirokova et al. in 2012.

There was no association found between PRP treatment and comorbidity of hypertension observed in an average patient of the study. Most of the patients (95 %) demonstrated high compliance with the treatment and completed the full course of PRP injections that also could be viewed as a strong argument in favor of the technique.

We acknowledge some limitations in our study. Our sample size is small with no controls with three intra-articular application of 0.9 % NaCl. However, the results from this study and the reported findings indicate to a favorable effect of PRP intra-articular injections applied for patients with grade 2 osteoarthritis of the knee.

CONCLUSION

Our findings suggest that intra-articular application of PRP in the treatment of patients with grade 2 osteoarthritis of the knee can provide pain control and functional improvement to a greater extent as compared to HA injections throughout the 6-month follow-up. Patients with grade 2 osteoarthritis of the knee showed high compliance with PRP intra-articular application (95 %).

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