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ORIGINAL ARTICLE

Demonstrating the effectiveness of Platelet Rich Plasma and Prolotherapy treatments in knee osteoarthritis

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Abstract

Background Platelet-rich plasma(PRP) and prolotherapy(PRL) are regenerative treatment approaches in the knee osteoarthritis (KOA).

Aim To see how efficient PRP and PRL are in treating KOA.

Methods A total of 108 patients with a diagnosis of KOA who received either PRL, PRP, or exercise therapy and whose 3-month follow-up data were available were included in this retrospective study (PRL $n=35$ or PRP $n=35$, exercise $n=38$). Visual Analogue Scale(VAS) and The Western Ontario McMaster University Osteoarthritis Index(WOMAC) were used as outcome measures at baseline, 1 month, and 3 months.

Results There were no statistically significant differences between the three groups in terms of demographic parameters, baseline assessments of pain intensity, or WOMAC scores. At the first and third months, all groups showed a substantial improvement in the VAS activity, resting and WOMAC values as compared to before treatment($p<0.05$). When the groups were compared, the VAS activity, resting, and WOMAC values in PRP and PRL improved significantly in the first and third months compared to the exercise group. At one month, there was a statistically significant improvement in VAS activity and WOMAC pain and total scores compared to PRP and PRL, but this improvement was not significant at 3 months.

Conclusion Pain and disability were significantly improved with PRL and PRP compared with exercise therapy. Although PRP is more effective than PRL in the first month after treatment, PRL may be preferred due to its low cost, long-term efficacy, and low complication rates due to the periarticular application.

Keywords Knee osteoarthritis · Platelet-rich plasma · Prolotherapy

Introduction

Osteoarthritis (OA) is a disease marked by the deterioration of articular cartilage integrity and subchondral bone sclerosis, resulting in joint pain, stiffness, limitation of movement, crepitation, effusion, and inflammation, as well as a reduction in daily activities and functionality and a reduction in quality of life [1–3]. OA is the most common joint disease that affects people of all ethnicities and cultures. The predicted rate of radiographic knee OA in adults over 60 years old in the USA was reported to be 37% [4, 5].

Although the etiopathogenesis is not fully understood, there is a lot of evidence showing that OA is a disease that covers not only the articular cartilage but also all joint structures (subchondral bone, joint capsule, synovium, menisci, tendons, ligaments) [2]. However, it is supported by evidence that OA is a chronic inflammatory process that progresses with attacks of low-severity inflammation due to increased

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cytokine and metalloproteinase [6]. In its treatment, it reduced the complaints of the patients, to increase the functions, to reduce the decrease in the quality of life, the losses in the workforce, and the burden of health expenditures. Although there are generally recommended and accepted treatment methods for OA, there is no treatment method accepted as the gold standard alone [7, 8]. When systematic literature is reviewed, it has been reported that no treatment has significant modifying properties and long-term efficacy [9–14]. This has brought alternative treatments to the agenda, and new studies on alternative treatments have been reported [5, 12–15].

Knee osteoarthritis (KOA) can be treated with both invasive and non-invasive treatments. Physical and rehabilitation therapy, nonsteroid antiinflamatuar drugs (NSAIDs) and glucosamine, intra-articular injection of hyaluronic acid, corticosteroid, platelet-rich plasma (PRP), and prolotherapy (PRL) are all non-invasive therapeutic options [16, 17]. Injectable medicines that produce regenerative changes in tissue structure and relieve OA symptoms are essential. PRL and PRP are essential regenerative injectable drugs since they are both reconstructive and preventative against replacement procedures [18].

PRL, which is the oldest regenerative treatment method, is the injection of a stimulant solution into the ligaments and into the joint to strengthen injured or weakened ligaments or other joint support structures that are the source of chronic pain [19]. PRL is an injectable treatment for chronic musculoskeletal injury, such as osteoarthritis of the knee [3, 10]. Although the exact mechanism of PRL action is unknown, it is assumed that hypertonic dextrose induces inflammation, ligament mass and strength, tendon hypertrophy, extracellular matrix production, fibroblastic proliferation, and articular cartilage regeneration [19, 20]. The extracellular glucose concentration increases with prolotherapy injections which cause cells to proliferate and produce PDGF, TGF-β, EGF, fibroblast growth factor, ILGF, and CTGF. These growth factors provide repair of tendons, ligaments, and other soft tissues [11, 21].

PRP, on the other hand, is the process of separating the blood taken from the patient into its components by undergoing a special centrifugation process and returning the obtained "platelet-enriched plasma" to the same patient by injection. The aim is to stimulate the healing mechanisms of damaged cartilage and soft tissues and to trigger regeneration [22, 23]. Platelets continue the inflammatory process by discharging some substances they store in their granules into the environment and play an active role in the wound healing process [24].

This research aimed to see how effective PRP and PRL treatments, two regenerative therapeutic modalities, were in treating knee osteoarthritis. In this approach, we hoped to add to the literature by evaluating the effects of regeneration treatment methods in knee osteoarthritis and determining if one treatment method was superior to the other.

Methods

A total of 576 male and female patients diagnosed with knee osteoarthritis between the ages of 18 and 65 were screened between March 2021 and January 2022. Before starting this retrospective study, approval for the study was obtained from the national ethics committee of Kanuni Sultan Süleyman Training Research Hospital (KAEK 2022.02.14). Inclusion criteria were to be between the ages of 18 and 65, diagnosed with knee osteoarthritis according to the Kellgren–Lawrence classification, and to have been applied one of the PRP or PRL treatment methods for a single knee at least 3 times (0, 2 weeks, 4 weeks) with 2 weeks intervals in terms of pain and disability management of knee osteoarthritis. Availability of post-treatment, first and third-month data. Exclusion criteria, knee operation history, malignancy, presence of any disease other than knee osteoarthritis that may cause knee pain (rheumatism, infection, trauma..), the patients who received any intraarticular injection treatments or physical therapy program in the last 12 months.

Four hundred seven of 576 patients, who had a history of previous knee operations, diagnosed with malignancy and rheumatic disease, could not access a knee X-ray, and received any intraarticular injection treatments or physical therapy program in the last 12 months were excluded. Of the 47 patients treated with PRP, 12 patients who did not receive PRP treatment a total of 3 times every 2 weeks and could not reach 3-month data were excluded, and a total of 35 patients were included in the PRP group. Of the 52 patients treated with PRL, 17 patients who did not receive PRL treatment a total of 3 times every 2 weeks, whose 3-month data could not be accessed, were excluded, and a total of 35 patients were included in the PRL group. Of the 70 patients treated with exercise, 32 patients whose 3-month data could not be accessed were excluded, and a total of 38 patients were included in the exercise group.

VAS activity and resting pain were evaluated in the first and third months after the treatment. WOMAC scores were also recorded. The VAS scale is a ruler-shaped line with values ranging from 0 to 10, with 0 indicating no pain, 5 indicating moderate pain, and 10 indicating severe pain. It consists of the patient's scored for the last 48 h of activity, resting and nighttime pain and stiffness.

WOMAC, a quality of life scale specific to OA, most frequently used in KOA and an OA-specific quality of life scale, has been increasingly accepted in the evaluation of patients with osteoarthritis since it was created in 1982. Tuzun et al. conducted a validity and reliability research in Turkey in 2005 [25]. WOMAC evaluates the patient's pain, stiffness, and functional status (physical function) in three separate subsections, the possible WOMAC score is between 0 and 96 [17].

Hackett's approach was used to provide PRL injections periarticularly, injecting dextrose into the fibro-osseous junction of ligaments or tendons [26]. 0.5 mL of 5% dextrose solution was injected subdermally into the medial collateral ligament, pes anserine attachment, tibial tuberosity, coronary ligaments, patella, and lateral collateral ligament. At each ligament-bone insertion, dextrose solution was injected using a peppering and skin sliding approach with a 25-gauge needle.

Each patient had 10 cc of venous blood collected for PRP. The centrifugation method we utilized has biphasic features, and we used two tubes, A and B. Two Na-citrate tubes were inserted in a centrifuge on opposite sides and spun for 10 min at 2000 rpm. Three layers were formed after the initial centrifugation. The bottom layer had several erythrocytes, the middle layer was buffy-coat (leukocyte + platelet), and the top layer was plasma. Using a 3 cc injector, the buffy coat and plasma obtained after centrifugation were transferred to the B tube. With 10% calcium chloride present in the tube, activation was conducted by flipping it upside down. For the second centrifugation process, the tubes were taken to the device and reprocessed at 4000 rpm for 5 min to obtain PRP. The obtained PRP was applied intraarticularly with a superolateral approach.

The workout program included quadriceps isometric strengthening, hamstring and quadriceps stretching, and short arc terminal extension movements. Patients who applied to the same exercise program were selected. The exercises were given to the patients by creating a template. It was recommended to apply the exercise program as one set, 10 repetitions per day.

Statistical analysis

IBM SPSS Statistics for Windows, Version 25.0, was used to conduct statistical analysis on all of the study data. The mean, standard deviation (SD), median (min–max), or number and frequency was used to convey descriptive data. The Shapiro–Wilk test was used to check the distributions of the variables. When appropriate, the Friedman test was used to compare groups, followed by the Bonferroni-corrected Wilcoxon signed-rank test or repeated measures analysis of variance (ANOVA), and finally, the Bonferroni post-hoc test. One-way ANOVA, Kruskal–Wallis, and chi-square tests were used to compare groups. To demonstrate statistical significance, a $p < 0.05$ value was accepted.

Prior power analysis of the study was performed using the "G.Power-3.1.9.2" program. In the calculations, ANOVA repeated measures between factor, effect size, 0.25, alpha 0.05, power 0.80, number of groups 3, number of measures 3, and total sample number was calculated as 108.

Table 1 Demographic and clinical characteristic of the participants

	PRP	PRL	EXE	P
Sex **F (%)** **M (%)**	30 (85.7) 5 (14.3)	29 (82.9) 6 (17.1)	29(76.3) 9(23.7)	0.568[a]
Age	55.22 + 6.18	52.97 + 5.99	51.36 + 12.25	0.176[b]
BMI	29.64 + 4.48	27.63 + 3.53	29.40 + 4.32	0.094[c]
VAS rest	2.97 + 2.12	2.91 + 1.48	2.84 + 1.96	0.958[b]
VAS activity	6.97 + 1.15	6.85 + 1.11	6.88 + 1.00	0.599[c]
WOMAC pain	13.25 + 2.82	13.02 + 3.20	12.92 + 3.14	0.895[c]
WOMAC Stiffness	5.11 + 1.20	5.01 + 1.33	4.84 + 1.36	0.658[b]
WOMAC functional	45.31 + 8.47	44.52 + 7.23	41.97 + 6.24	0.150[c]
WOMAC total	63.68 + 10.99	62.61 + 9.84	59.73 + 7.17	0.182[c]

[a]Chi-Square test

[b]One-way ANOVA

[c]Kruskal–Wallis test

PRP platelet rich plasma, *PRL* prolotherapy, *EXE* exercise, *F* female, *M* male, *BMI* body mass index

Results

This research included a total of 108 patients. PRP, PRL, and exercise therapy were used to separate the patients into three groups. There were no statistically significant differences between the three groups in terms of demographic parameters (age and gender), baseline assessments of pain intensity, or WOMAC scores (Table 1).

At the first and third months after therapy, all three groups showed a substantial improvement in VAS activity, resting, and WOMAC values as compared to before treatment ($p < 0.05$). When the groups were compared, the VAS activity, resting, and WOMAC (pain, stiffness, function) values in PRP and PRL improved significantly in the first and third months when compared to the exercise group. At 1 month, there was a statistically significant improvement in VAS activity, WOMAC pain, and WOMAC total scores when compared to PRP and PRL, but this improvement was not significant at the third month (Table 2, Fig. 1).

Discussion

In this retrospective study, which demonstrated the effectiveness of two regenerative treatment methods in knee osteoarthritis, an improvement in pain and functionality was found in the PRP and PRL groups compared to exercise in the first and third-month evaluations. In the short term, better pain control was achieved with PRP, and no superiority was found over each other in the long term.

Table 2 Post-treatment comparisons of VAS and WOMAC scores

	BT	PostT 1 month	PostT 3 month	*p* (Friedman)	Difference BT-PostT 1	*p* (Kruskal–Wallis)	Difference BT-PostT 3	*p* (Kruskal–Wallis)
VAS activity						< 0.001		< 0.001
PRP	6,97 ± 1.15	3.71 ± 1.65	2.88 ± 2.06	< 0.001	3.25 ± 1.65	< 0.001[a]	4.08 ± 1.80	< 0.001[a]
PRL	6.88 ± 1.00	4.41 ± 1.59	3.64 ± 1.66	< 0.001	2.47 ± 1.98	0.021[b]	3.23 ± 1.93	0.039[b]
EXE	6.71 ± 1.18	5.23 ± 1.60	4.50 ± 2.34	< 0.001[d]	1.47 ± 1.51	0.047[c]	2.21 ± 1.97	
VAS rest						0.005		0.008
PRP	2.97 ± 2.12	0.97 ± 0.98	0.45 ± 0.65	< 0.001	2.02 ± 1.49	0.004[a]	2.51 ± 1.80	= 0.003[a]
PRL	2.91 ± 1.48	1.32 ± 1.47	0.70 ± 0,93	< 0.001[d]	1.58 ± 1.68	0.027[b]	2.20 ± 1.57	= 0.034[b]
EXE	2.84 ± 1.96	2.02 ± 2.22	1.55 ± 1.79	< 0.001	0.81 ± 1.29		1.28 ± 1.76	
WOMAC Total						< 0.001		< 0.001
PRP	63,68 ± 10.99	32.74 ± 10.07	24.17 ± 8.42	< 0.001	30.94 ± 9.89	< 0.001[a]	39.51 ± 9.88	< 0.001[a]
PRL	59,73 ± 7.17	49.34 ± 18.69	42.50 ± 18.35	< 0.001	10.39 ± 16.44	< 0.001[b]	17.23 ± 15.61	< 0.001[b]
EXE	62.61 ± 9.84	38.11 ± 10.06	28.17 ± 10.84	< 0.001	24.50 ± 9.69	0.033[c]	34.44 ± 10.64	

[a]PRP and exercise

[b]PRL and exercise

[c]PRP and PRL

[d]Repeated measure ANOVA

BT before treatment; *PostT* post treatment

In present study, PRL treatment was applied periarticularly, while PRP was applied intraarticularly. Although better improvements were detected in pain with PRP treatment in the short term, it is thought that intra-articular application is more effective on pain; a small study found no significant differences in WOMAC and VAS scores between patients treated with intraarticular and periarticular prolotherapy [27]. Similar results were found between periarticular administration and intraarticular PRL administration in the Zahra Rezasoltani study [28]. It should be kept in mind that the risks of complications are avoided with the periarticular application, which has a similar effect on pain and disability.

The particular molecular targets for periarticular PRL's impact are unknown. Injections into the periarticular space around the knee joint trigger an inflammatory response in the joint capsule. Infiltrating inflammatory cells and cytokines into the periarticular area can boost blood flow to the capsular joint, improve cartilage nutrition, and speed up regeneration. Hypertonic dextrose may enhance the healing of chronically damaged peri- and intra-articular tissue by boosting inflammatory cytokines, according to one theory [25, 29]. The specific mechanism of prolotherapy is unknown, although it is expected to cause a pro-inflammatory reaction, which releases growth factors and cytokines, and eventually to a regenerative process within the afflicted joint. Injecting a hyperosmolar dextrose solution into nociceptive pain fibers may also hyperpolarize them by driving potassium channels open, resulting in diminished pain perception [30]. Periarticular dextrose injection has been found in animal experiments to improve healing by causing vascular and fibroblast proliferation as well as cartilage thickening. When compared to exercise, Sit et al. found that PRL resulted in lower WOMAC ratings in patients with knee OA [31].

PRP is a regenerative medicine product that is manufactured to have a higher platelet concentration than in vivo plasma. It is generally agreed that platelet concentration that in PRP should be between 2 and 8 times that of autologous serum platelets. When platelets are activated, they quickly release a vast number of growth factors from their granules, including TGF- and IGF-1 [32, 33]. Due to one- or two-turn centrifugation of autologous patient blood, PRP yields either leukocyte-poor (LP) or leukocyte-rich (LR) PRP content. LR-PRP was used in our study. There is no obvious benefit to using LP-PRP or LR-PRP in the literature; however, adverse events seem to be more common with LR-PRP [32]. Although retrospective in our study, no significant side effects were reported except for temporary side effects such as pain, redness, and swelling. In the literature, there is no established protocol, and the results of our study will contribute to the literature.

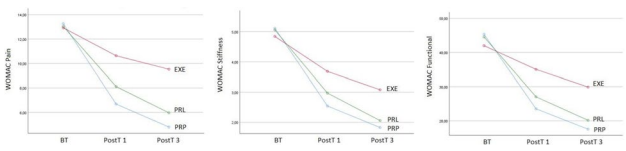

Fig. 1 WOMAC score changes during follow-ups according to groups

About 2 months after injection, PRP begins to provide pain relief and can last up to 12 months [27, 32–34]. In present study, better improvement in pain and enegliness was found with PRP compared to PRL. Rahimzadeh et al. found better improvement in disability and pain compared to PRP and PRL, similar to our study [18]. There are many studies in the literature evaluating the effectiveness of PRP in knee OA. I-PRP gives better results in younger patients with early KOA [32, 33]. Similar to the results of our study, the superiority of PRP over PRL in pain control has also been shown in the literature over hyaluronic acid (HA), which is often used for treating KOA. In a study comparing PRP and HA, Chang et al. found that PRP was more effective in terms of pain in KOA compared to ha [33]. In 9 of the 11 studies analyzed, Laver et al. found a definite benefit for PRP over HA for knee OA [27, 33]. Patients who received PRP had considerably lower WOMAC scores than those who received HA, according to Meheux et al. [34].

In the case of KOA, PRL is an effective therapy option. Rabago et al. discovered that dextrose improved pain relief, edema, and range of motion much more than lidocaine injections or exercise in a three-arm, randomized controlled, double-blind research [3]. A substantial decrease in WOMAC scores in KOA was identified in a research by Dumais et al. that incorporated PRL and exercise therapy [35]. In a single-arm prospective trial, Eslamian and Amouzandeh demonstrated the long-term effects of dextrose PRL. In patients with moderate KOA, intra-articular injections of dextrose produced significant therapeutic effects of PRL. WOMAC scores showed that pain intensity decreased at rest and rose during the activity, but range of motion increased. Improvements were still visible 6 months later [36]. Hashemi et al. tested the efficacy of dextrose against ozone in two groups of 40 patients with mild-to-moderate KOA in a randomized controlled trial. Both groups received intra-articular injections, which were given three times with a 10-day interval between treatments. The VAS and WOMAC scores improved significantly before treatment and 3 months after treatment, although they were not statistically different for both groups [37]. In our study, it has been shown that PRL applied in a periarticular manner, similar to the literature, is effective in terms of pain and disability in knee osteoarthritis in a 3-month follow-up. This effect is superior in exercise treatment. The beneficial results in this study could be explained by a combination of needle trauma, dextrose-specific effects, and volume expansion.

This study had some limitations, including the fact that it was a retrospective study with no control group receiving placebo, lack of morphological examination of cartilage, soft tissue, and structures in and around the knee joint, a small sample size, and a short duration for patient assessment. Also, exercise compliance could not be determined because it was a retrospective study. Strength of the study is that it compares regenerative treatment methods, has an exercise group, and includes a 3-month follow-up.

Conclusion

In this study, pain and disability were significantly improved with dextrose PRL and PRP compared with exercise therapy. In the first month evaluation, PRP injections reduced pain and functional limitations better than PRL injections in participants with KOA. But this effect could not be detected in the long term. Although PRP is more effective than PRL in the first month of evaluation, it may be preferred because of its low cost, long-term efficacy, and low complication rates due to the periarticular application. Additionally, studies can be designed by injecting PRP solution into the fibro-osseous junction of ligaments or tendons to compare the effects of PRL and PRP treatment.

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Declarations

Research involving human and animal participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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