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Platelet-rich plasma and dextrose prolotherapy in osteoarthritis knee

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ABSTRACT

Background: A prevalent but little-understood ailment is osteoarthritis (OA) knee. It is a typical issue in daily practice. Due to the non-reversible pathophysiology of OA, treating OA knee is difficult, and physical therapy is the cornerstone of treatment. In the literature that is currently available, no crystal-clear management protocol is given. In this modest endeavor, the role of injections of Dextrose Prolotherapy (PRL) and platelet-rich plasma (PRP) in OA of the knee joint is evaluated. **Aims and Objectives:** The current study was designed to establish, the role of injections of Dextrose PRL and PRP in OA of the knee joint. **Materials and Methods:** The total study size consisted of 99 participants who were split into three groups at random: PRP + Physical Therapy (Group A, 33 participants), Dextrose PRL + Physical Therapy (Group B, 33 participants), and Physical Therapy alone (Group C, 33 Participants). The Western Ontario McMasters University OA index (WOMAC) and knee pain scale composite score were used to assess the primary end measure, which was the change in knee-related quality of life and pain. **Results:** There were no significant differences in Group A's (66.58), Group B's (63.06), and Group C's (64.48) baseline WOMAC scores in our study ($F = 1.189$, $P = 0.3090$). Group A had the lowest WOMAC score at 6 months (50.48), followed by Group B (53.70) and Group C (59.27), indicating that the effects of the treatment varied ($F = 7.591$, $P = 0.0009$*). The highest improvement was seen in Group A from 3 to 6 months (6.70–12.09), with substantial intergroup differences ($F = 81.11$ at 3 months, $F = 154.6$ at 6 months; both $P < 0.0001$). **Conclusion:** Two promising treatments for knee OA are PRP and dextrose PRL. This study demonstrates that Platelet-rich plasma (PRP) and dextrose prolotherapy (PRL) offer promising, non-surgical treatments for knee osteoarthritis, alleviating symptoms and enhancing quality of life without lengthy drug regimens.

Key words: Osteoarthritis knee; Platelet-rich plasma; Dextrose prolotherapy; Physical therapy; Western Ontario McMasters University osteoarthritis index; Knee pain scale

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INTRODUCTION

Knee osteoarthritis (OA) is a long-lasting and progressive joint condition that leads to substantial disability and adversely affects the quality of life for both individuals afflicted and their caregivers. This prevalent disorder presents considerable societal and economic challenges. It is frequently observed in adults, with a significant 45% likelihood of experiencing symptomatic knee OA at some point in their lives.[1] Recent research has called into question the conventional belief that OA is solely a result of joint degeneration, uncovering a more complex pathogenesis. Current understanding indicates that OA encompasses a variety of processes that extend beyond simple degeneration.[2] The acknowledgment that OA currently has no definitive cure has prompted the investigation

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of innovative treatment strategies. Current therapeutic approaches mainly focus on alleviating symptoms and improving joint functionality, rather than preventing the progression of the disease. Research is actively exploring a range of disease-modifying therapies designed to control cartilage degradation and regeneration, address inflammation, and alter the structure of subchondral bone.[3] Recently, several injection-based treatments for knee OA have been evaluated. These include dextrose prolotherapy (PRL), ozone therapy, botulinum toxin injections, platelet-rich plasma (PRP) therapy, and hyaluronic acid injections.[4-7]

PRP is a formulation derived from autologous plasma that has been enriched to contain a higher concentration of platelets than what is typically found in whole blood.[8] The justification for utilizing this high platelet concentration lies in their ability to release and supply an elevated quantity of essential growth factors and cytokines from their alpha granules, thereby providing a regenerative stimulus that enhances healing and facilitates repair in tissues characterized by low healing capacity.[9] Beyond their primary function in hemostasis, platelets play several key roles within the body. For instance, they attract white blood cells to injury sites after tissue damage and safeguard damaged cells from infection. In addition, platelets contain growth factors like platelet-derived growth factor (PDGF) and basic fibroblast growth factor which promote stem cell production.[9] These attributes make platelets appealing for OA treatment. Several trials have suggested the efficacy of PRP to improve functional outcome for mild knee OA.

PRL is a treatment for chronic musculoskeletal pain that involves the administration of injections. It is recognized as a form of regenerative injection therapy[10] however, it is distinct from other such therapies, including PRP and stem cell injections, due to the lack of a biological agent. The most frequently utilized solution in PRL is hypertonic dextrose, which has demonstrated positive results in numerous clinical trials.[11] This treatment is cost-effective, easily accessible, easy to perform, and has been reported to be safe.

A recent investigation conducted by Topol and associates[12] employed video-arthroscopy documentation both before and after treatment to assess the denuded femoral cortex surfaces for signs of cartilage regeneration in knees affected by OA. PRL, which involves the use of dextrose, is gaining recognition as a viable injection-based therapy for the management of chronic painful musculoskeletal disorders. This treatment is thought to trigger a localized inflammatory response, which in turn fosters tissue proliferation and remodeling, thereby aiding in the healing process.[13]

Despite numerous reports highlighting clinical success in treating various musculoskeletal conditions, dextrose PRL has yet to be recognized as a standard treatment for knee OA in current guidelines. For example, the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of OA of the Hand, Hip, and Knee conditionally recommended against the use of PRL for patients suffering from knee OA.[14] Similarly, the OA research society international guidelines strongly advise against dextrose PRL, citing a lack of robust evidence to substantiate its effectiveness.[15] Nevertheless, randomized trials investigating PRL have continued to emerge in recent years, with a significant increase in relevant literature. Most reviews have suggested potential positive outcomes of PRL across various functional aspects of OA.[16,17]

In summary, both PRP and dextrose PRL present themselves as promising alternatives for the treatment of knee OA. These minimally invasive procedures have the potential to reduce pain and improve functionality by harnessing the body's natural healing processes. Although additional studies are required to gain a complete understanding of their long-term efficacy and the best methods of application, they represent valuable enhancements to the range of therapeutic options available for OA. Given their ability to alleviate symptoms and improve quality of life without the need for surgical intervention or extended medication use, PRP and dextrose PRL mark significant advancements in the pursuit of effective management strategies for OA.

Aims and objectives

The current study was designed to establish, the role of injections of Dextrose Prolotherapy and Platlet Rich Plasma (PRP) in osteoarthritis of the knee joint.

MATERIALS AND METHODS

This prospective observational study was carried out over a period of 18 months, from February 2023 to July 2024, following approval from the institutional ethics committee (Registration No. ECR/717/Inst./U.P./2015/RR-21) at a tertiary care center. A total sample size of 99 participants was determined and allocated into three groups: (PRP+Physical Therapy), (Dextrose PRL+Physical Therapy), and Physical Therapy alone (Control group), with each group consisting of 33 participants.

All individuals aged 18 years and older diagnosed with knee OA classified as Kellgren Lawrence (KL) Grade 1, 2, or 3 who presented at our facility and consented to participate in the study were included. Exclusion criteria encompassed patients with KL Grade 4, those who are pregnant, individuals with diabetes, patients undergoing

anticoagulation therapy, individuals with a history of total knee replacement, those who had received knee PRL previously, patients who had any knee injection within the last 3 months, individuals with inflammatory or post-infectious knee arthritis, those with allergies or intolerances to the study medication, individuals with a body mass index (BMI) exceeding 40 kg/m^2, and those unwilling to participate in the study.

The main outcome measure was the alteration in knee-related quality of life, evaluated through the composite score of the Western Ontario McMaster University OA Index (WOMAC). This validated questionnaire assesses the severity of OA by utilizing subscales for pain, stiffness, and function. The WOMAC composite score, which is derived as the weighted average of the three subscale scores, spans from 0 (indicating the worst quality of life) to 100 (indicating the best quality of life) and demonstrates responsiveness to change.

The knee pain scale (KPS), a validated tool for assessing the frequency of knee pain, was one of the secondary outcomes. It is a 0–4 ordinal scale, with zero denoting no pain, 1–3 mild pain, 4–6 moderate pain, 7–9 severe pain, and 10 worst pain. Higher scores indicate more severe symptoms. For both treated and untreated knees, KPS measurements were collected independently. The individual knee served as the KPS model's analytical unit. At each evaluation point, each participant filled out two KPS questionnaires, one for each knee, enabling individual KPS score analysis. The participant added two knees to the treated knees model in situations where both knees received treatment.

The WOMAC and KPS scores were obtained in person before any procedures at baseline, as well as at 3 and 6 months. Data were recorded in Microsoft Excel and analyzed using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Continuous variables were assessed using mean (standard deviation) or range values as necessary. Dichotomous variables were presented as numbers/frequencies and analyzed with the Chi-square test. To compare means across two or more groups, the analysis of variance (ANOVA) test was employed. A $P<0.05$ or 0.001 was considered statistically significant.

RESULTS

The age and gender distribution, and socioeconomic status of the patients enrolled in this study are presented in Tables 1 and 2, respectively.

Table 1: Age/sex distribution of the enrolled patients among the groups

Age distribution	Group-A		Group-B		Group-C		P-value
	n	%	n	%	n	%	
40–49	5	15.15	8	24.24	4	12.12	X=3.625 P=0.7273
50–59	15	45.45	15	45.45	16	48.48	
60–69	10	30.30	9	27.27	12	36.36	
70–79	3	9.09	1	3.03	1	3.03	
Sex distribution							
Female	20	60.61	16	48.48	21	63.64	X=1.737 P=0.419
Male	13	39.39	17	51.52	12	36.36	

Table 2: Socioeconomic status of the enrolled patients among the group

Socioeconomic status	PRP+physical therapy (group-A)		Dextrose prolotherapy+physical therapy (group-B)		Physical therapy only (control group) group-C		P-value
	n	%	n	%	n	%	
Auto driver	1	3.03	1	3.03	3	9.09	X=24.84 P=0.4146
Clerk	5	15.15	2	6.06	2	6.06	
Farmer		0.00	1	3.03		0.00	
Housemaid	4	12.12	1	3.03	4	12.12	
Housewife	10	30.30	7	21.21	10	30.30	
Labor	5	15.15	5	15.15	8	24.24	
Nurse	2	6.06	2	6.06	2	6.06	
Policeman	1	3.03	3	9.09	3	9.09	
Retired		0.00	1	3.03		0.00	
Rikshaw driver	2	6.06	5	15.15		0.00	
Teacher		0.00	2	6.06		0.00	
Watchman		0.00	1	3.03		0.00	
Worker	3	9.09	2	6.06	1	3.03	

PRP: Platelet rich plasma

OA grades enrolled in study

The percentages reflect the distribution of patients within each group who were assigned to each grade: Grade 1 (Group-A: 33.33%, Group-B: 27.27%, Group-C: 36.36%), Grade 2 (Group-A: 30.30%, Group-B: 33.33%, Group-C: 36.36%), and Grade 3 (Group-A: 36.36%, Group-B: 39.39%, Group-C: 27.27%). The statistical analysis reveals no significant differences in OA grades among the groups (X=1.384, P=0.8470). This finding indicates that the distribution of OA grades is similar across Group A, Group B, and Group C (Table 3).

At baseline, the average WOMAC scores were recorded as 66.58 (SD=10.49) for Group A, 63.06 (SD=8.88) for Group B, and 64.48 (SD=8.50) for Group C. The ANOVA demonstrated no significant differences among the groups at baseline (F=1.189, P=0.3090). After 3 months, a reduction in mean WOMAC scores was observed across all groups: Group A reported a mean score of 59.88 (SD=10.13), Group B had a mean score of 58.52 (SD=8.71), and Group C recorded a mean score of 61.42 (SD=8.45). Nonetheless, the differences among the groups at this time point were not statistically significant (F=0.8340, P=0.4374). By the 6-month evaluation, significant changes were noted. Group A exhibited the lowest mean WOMAC score of 50.48 (SD=10.51), followed by Group B with a mean score of 53.70 (SD=8.72), while Group C had the highest mean score of 59.27 (SD=8.45). The ANOVA results indicated a significant difference among the groups at this assessment (F=7.591, P=0.0009*), suggesting that the interventions or treatments had varying impacts on the WOMAC scores of the groups over the 6-month duration (Table 4).

At the initial assessment, the average KPS scores were recorded as 7.60 (SD=0.72) for Group A, 7.39 (SD=0.65) for Group B, and 7.68 (SD=0.70) for Group C. The ANOVA showed no statistically significant differences among the groups at this baseline measurement (F=2.250, P=0.2170). However, by the 3-month follow-up, notable changes were evident. The mean KPS scores declined for all groups: Group A reported a mean score of 6.05 (SD=0.82), Group B had a mean score of 6.30 (SD=0.67), and Group C recorded a mean score of 6.86 (SD=0.82). ANOVA indicated a significant difference among the groups at this time point (F=9.495, P=0.0002*), reflecting the differing effects of the treatments on the patients' performance status. At the 6-month evaluation, additional significant changes were observed. Group A had the lowest mean KPS score of 4.97 (SD=0.97), followed by Group B with a mean score of 5.36 (SD=0.69), while Group C achieved the highest mean score of 6.42 (SD=0.92). ANOVA confirmed a significant difference among the groups at this assessment (F=24.63, P<0.0001*), highlighting the distinct effects of the interventions on the patients' performance status over the 6-month duration (Table 5).

The improvements in the WOMAC scores for groups A, B, and C at the 3 and 6-month intervals indicate that Group A exhibited the most substantial enhancement at both time points, increasing from 6.70±1.19 at 3 months to 12.09±1.44 at 6 months. Notable intergroup differences were observed (F=81.11 at 3 months, F=154.6 at 6 months; both P<0.0001). In addition, t-tests highlighted significant advancements within each group (Group A: t=15.80, Group B: t=6.902, Group C: t=6.242; all P<0.0001) (Table 6).

The analysis of KPS scores indicated that Group A exhibited the most significant improvements at both the 3-month mark (1.24±0.43) and the 6-month mark (2.73±0.45), with substantial differences observed among the groups at each time point (F=10.65 at 3 months, F=128.2 at 6 months; both P<0.0001). Notable intra-group improvements were validated by high t-values (Group A: t=1311, Group B: t=10.59, Group C: t=3.406; all P<0.0001) (Table 7).

Table 3: Osteoarthritis grade in the enrolled patients among the group

OA Grade	Group-A		Group-B		Group-C		P-value
	n	%	n	%	n	%	
1	11	33.33	9	27.27	12	36.36	X=1.384
2	10	30.30	11	33.33	12	36.36	P=0.8470
3	12	36.36	13	39.39	9	27.27	

OA: Osteoarthritis

DISCUSSION

Numerous minimally invasive and non-invasive methods have been utilized in the management of knee OA. The most prevalent treatments include physical medicine and rehabilitation therapy, non-steroidal anti-inflammatory drugs,

Table 4: WOMAC score of the enrolled patients among the group at different follow-ups

WOMAC score	Group-A		Group-B		Group-C		P-value
	Mean	SD	Mean	SD	Mean	SD	
Baseline	66.58	10.49	63.06	8.88	64.48	8.50	F=1.189 P=0.3090
3rd Months	59.88	10.13	58.52	8.71	61.42	8.45	F=0.8340 P=0.4374
6th Months	50.48	10.51	53.70	8.72	59.27	8.45	F=7.591 P=0.0009*

WOMAC: Western Ontario McMasters University osteoarthritis index, SD: Standard deviation, F: F ratio, t: t statistics/value, P: P value. *statistically significant (Very strong evidence against the null hypothesis)

Table 5: KPS score of the enrolled patients among the group at different follow-ups

KPS score	Group-A		Group-B		Group-C		P-value
	Mean	SD	Mean	SD	Mean	SD	
Baseline	7.60	0.72	7.39	0.65	7.68	0.70	F=2.250 P=0.2170
3rd Months	6.05	0.82	6.30	0.67	6.86	0.82	F=9.495 P=0.0002*
6th Months	4.97	0.97	5.36	0.69	6.42	0.92	F=24.63 P<0.0001*

KPS: Knee pain scale, SD: Standard deviation, F: F ratio, P: P value. *statistically significant (Very strong evidence against the null hypothesis)

Table 6: Improvement in WOMAC score of the enrolled patients among the group at different follow-ups

WOMAC score	Group-A	Group-B	Group-C	P-value
Improvement at 3 months	6.70±1.19	4.55±1.33	3.06±0.95	F=81.11 P<0.0001*
Improvement at 6 months	12.09±1.44	7.36±1.79	5.21±1.63	F=154.6 P<0.0001*
P-value	t=15.80 P<0.0001*	t=6.902 P<0.0001*	t=6.242 P<0.0001*	

WOMAC: Western Ontario and McMaster universities arthritis index, F: F ratio, t: t statistics/value, P: P value. *statistically significant (Very strong evidence against the null hypothesis)

Table 7: Improvement in KPS score of the enrolled patients among the group at different follow-ups

KPS score	Group-A	Group-B	Group-C	P-value
Improvement at 3 months	1.24±0.43	1.09±0.29	0.82±0.39	F=10.65 P<0.0001*
Improvement at 6 months	2.73±0.45	2.03±0.39	1.15±0.36	F=128.2 P<0.0001*
P-value	t=1311 P<0.0001*	t=10.59 P<0.0001*	t=3.406 P<0.0001*	

KPS: Knee pain scale, F: F ratio, t: t statistics/value, P: P value. *statistically significant (Very strong evidence against the null hypothesis)

and glucosamine. Should these initial strategies fail to yield satisfactory results, intra-articular injections of hyaluronic acid, corticosteroids, PRP, PRL, and growth hormone, along with radiofrequency interventions, have been explored.[18,19] Extensive research has been conducted to evaluate the effectiveness of PRP therapy in alleviating the symptoms and discomfort associated with OA. Notable studies by Patel et al.,[20] Gobbi et al.,[21] Kim et al.,[22] and Sampson et al.,[23] have contributed to this body of knowledge. Activated platelets release various growth factors and cytokines, and *in vivo* studies suggest that PRP may promote chondrocyte differentiation and proliferation. In addition, PRP may inhibit the Nuclear factor-kappa B pathway, potentially offering anti-inflammatory benefits.[24] The PRP solution typically contains 1.5–2 million platelets per milliliter, resulting in a five-fold increase in growth factors and platelets. As a PRL agent, hyperosmolar dextrose elevates PDGF levels, and its irritative properties have been shown to facilitate the repair of connective tissue injuries. However, PRP therapy has been found to be less effective than PRL in reducing inflammation and addressing enthesitis conditions.[17] Recent studies indicate that PRP can significantly alleviate pain and improve quality of life when compared to dextrose PRL over time. Rahimzadeh et al.,[19] utilized the WOMAC as an outcome measure in their research. By the conclusion of their study, PRP injections demonstrated greater efficacy in reducing pain, stiffness, and functional limitations.

In our intervention results, the baseline WOMAC scores for Group A (66.58), Group B (63.06), and Group C (64.48) were found to be comparable, with no significant differences identified (F=1.189, P=0.3090). Following a 3-month duration, the average WOMAC scores were recorded as 59.88 for Group A, 58.52 for Group B, and 61.42 for Group C, again showing no statistically significant differences among the groups (F=0.8340, P=0.4374). At the 6-month mark, Group A exhibited the lowest WOMAC score of 50.48, while Group B and Group C had scores of 53.70 and 59.27, respectively, indicating differing treatment effects (F=7.591, P=0.0009*). Significant intergroup differences were observed (F=81.11 at 3 months, F=154.6 at 6 months; both P<0.0001), with Group A demonstrating the most substantial improvement from 3 to 6 months (from 6.70 to 12.09). T-tests conducted within each group revealed significant enhancements (Group A: t=15.80, Group B: t=6.902, Group C: t=6.242; all P<0.0001), indicating varied treatment responses throughout the 6-month study period. The dynamic nature of the WOMAC score improvements is evident, with Group A's response to the intervention being significantly superior to those of Groups B and C. Similarly, the findings of Rahimzadeh et al.,[19] indicated that over a 24-week period, PRP therapy was more effective than PRL in reducing WOMAC scores, with significant improvements noted at various intervals. Their study demonstrated that PRP therapy led to a considerable overall enhancement in WOMAC scores, suggesting it may be a more effective treatment option for knee OA symptoms compared to alternative therapies. These differences underscore the variability in treatment outcomes and emphasize the potential benefits of PRP therapy for patients suffering

from knee OA. PRP injection therapy can safely and effectively improve functional activity in patients with OA and produce positive analgesic effects in patients with Knee OA,[25] Temporomandibular joint OA, and Ankle OA. However, PRP injection therapy did not significantly reduce pain symptoms in patients with Hip OA.[26,27]

Dextrose PRL shows promising potential in reducing joint pain and stiffness while enhancing functional performance in individuals with knee OA though existing studies are at high risk of bias. This treatment may be considered as an option. It is generally safe and could be explored for patients with limited alternatives. Future studies should incorporate follow-up periods to better assess the duration of its effects and inform treatment decisions.[28,29]

Baseline KPS scores were observed in Groups A, B, and C of our study, indicating an initial equivalence among the participants. However, after a period of 3 months, significant differences emerged in the reductions of KPS scores across the groups, suggesting that the therapies affected them in distinct ways ($F=9.495$, $P=0.0002$*). By the 6-month mark, Group A exhibited the most substantial improvement in KPS scores compared to Groups B and C, underscoring the treatment's significant effect ($F=24.63$, $P<0.0001$*). These findings align with the research conducted by Rabago et al.,[30] which demonstrated that dextrose PRL led to improvements in WOMAC and KPS scores over a 52-week duration, emphasizing the potential for long-term efficacy in treating knee OA.

A comprehensive analysis of treatment-related, clinical, and demographic factors across three distinct groups of patients with OA underscores the study's credibility and relevance. The results indicated that the baseline characteristics were initially comparable, as there were no significant differences in socioeconomic status, BMI, age distribution, or gender among the groups. However, marked differences in the duration of diabetes were observed, suggesting potential implications for the management strategies employed. Importantly, while the initial functional levels and severity of OA were similar across the groups, Group A exhibited the most pronounced variability in treatment outcomes over time. These findings emphasize the importance of personalized treatment approaches and ongoing monitoring to enhance therapeutic effectiveness and improve patient well-being. Future research should further explore these dimensions to refine treatment methodologies and elevate the standard of care in OA management.

Limitations of the study

This study's limitations include a small sample size and limited follow-up duration, which may impact the generalizability of the findings. Further research is needed to confirm the long-term efficacy of PRP and dextrose prolotherapy.

CONCLUSION

Both PRP and Dextrose PRL offer potential benefits for knee OA when standard treatments fall short. PRP tends to be more effective but is also more expensive and may cause more injection-site discomfort. Dextrose PRL is generally safe and could be explored for patients with limited alternatives. Because patients respond differently, treatment should be tailored to the individual. Larger, more diverse studies are needed to confirm these findings.

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YPV- Definition of intellectual content, literature survey, implementation of study protocol, data collection, data analysis, manuscript preparation; **AAK-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **YVS-** Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, Review Manuscript, manuscript revision and submission of article; **AP-** Literature survey, preparation of tables and review manuscript; **AS-** Review manuscript; **ISK-** Review manuscript; **NS-** Review manuscript.

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