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Original Research Article

Is More Always Better? A Comparative Study of Single versus Multi-dose Intra-articular PRP Injections in the Management of Knee Osteoarthritis

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Abstract:

Knee osteoarthritis (OA) is a leading cause of disability worldwide, driving a search for treatments that do more than just manage symptoms. Platelet-rich plasma (PRP) has emerged as a frontrunner in regenerative medicine, utilizing concentrated growth factors to stimulate tissue repair. However, a significant gap remains in clinical guidelines regarding the optimal dosing protocol.

This prospective comparative study evaluated 90 patients with early to moderate (Kellgren-Lawrence Grade I-II) knee OA to determine if multiple injections provide superior outcomes to single-dose regimens. Participants were divided into three groups: Group A (single injection), Group B (two injections), and Group C (three injections), with multi- dose intervals set at two weeks.

The results revealed that while all groups experienced significant initial relief at 6weeks, their paths diverged significantly by the 6-month mark. The triple-dose group demonstrated a 60.5% improvement in pain (VAS scores), whereas the single and double-dose groups saw their improvements taper off to 27.4% and 30.1% respectively. Functional assessments via the WOMAC index mirrored these findings, with Group C maintaining sustained improvement while Groups A and B showed partial deterioration from their peak. Ultimately, the study concludes that a three – dose PRP regimen is safe and significantly more effective for achieving long term therapeutic benefits in knee OA management.

Objective: The primary objective of this research was to investigate the dose- responserelationshipofintra-articularPRPinjectionsinpatientswith early-stage knee osteoarthritis. Specifically, the study aimed to:

- Compare the clinical effectiveness of single, double, and triple-dose PRP protocols.
- Evaluate the durability of pain relief and functional recovery over a six-month period.
- Assess the safety and tolerability of repeated injections.
- Validate the hypothesis that a triple-dose regimen provides superior sustained benefits compared to fewer injections.

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Introduction

Knee OA is a degenerative condition characterized by the breakdown of joint cartilage, leading to pain, stiffness, and loss of mobility. With an aging population, the prevalence and economic burden of this condition are rising sharply. Traditional treatments, such as NSAIDs or corticosteroids, often provide only temporary relief and do not address the underlying pathology.

Platelet-Rich Plasma (PRP) therapy represents a shift toward biologic disease modification. By delivering a high concentration of platelets—3 to 5 times above baseline—to the joint, PRP releases growth factors that modulate inflammation and potentially encourage cartilage remodeling. While its efficacy over placebo is well-documented, the clinical community lacks consensus on whether a single bolus is sufficient or if a series of "booster" injections is required to maintain the therapeutic window.

Discussion and Clinical Implications: The findings of this study suggest that the "More is Better" hypothesis holds true for PRP therapy in

early-stage knee OA. The superiority of the triple-dose regimen over single and double doses likely stems from the temporal kinetics of growth factor release.

- **Sustained Bioactivity:** While a single injection provides an initial bolus of bioactive factors to initiate the healing cascade, these factors are metabolized and cleared from the joint environment over time.
- **Cumulative Effect:** Multiple injections at two-week intervals presumably maintain therapeutic growth factor concentrations for a longer duration, allowing for more comprehensive tissue remodeling and prolonged anti-inflammatory effects.
- **Alignment with Literature:** These results align with systematic reviews, such as those by Vilchez-Cavazos et al., which concluded that multiple PRP injections provide significantly better clinical outcomes at 6-month follow-ups.
- **Optimal Balance:** A three-injection protocol appears to represent an optimal balance between maximizing therapeutic efficacy and minimizing the treatment burden on the patient.

Materials and Methods

Patient Population and Selection: The study enrolled 90 participants aged 35–65 years with symptomatic knee OA.

- **Inclusion:** Radio graphically confirmed Kellgren-Lawrence Grade I-II OA.
- **Exclusion:** Advanced OA (GradeIII-IV), knee mal alignment>5°, recent intra-articular injections (within 6 months), or systemic inflammatory conditions.

Patient Demographic and Clinical Characteristics: This table shows the baseline comparability across the three treatment groups, confirming that the participants had similar characteristics before receiving treatment.

Table 1: Patient Demographic and Clinical Characteristics

Characteristics	Single Dose (n=30)	Double Dose (n=30)	Triple Dose (n=30)	P-Value
Mean Age (Years)	51.8 ± 7.9	51.3 ± 8.4	53.1 ± 8.4	0.742
Gender (Female %)	73.30%	70.00%	70.00%	0.826
Mean BMI (kg/m²)	27.9 ± 3.8	28.5 ± 3.2	28.5 ± 3.2	0.691
KL Grade 1 (Early OA)	46.70%	53.30%	53.30%	0.873
KL Grade 2 (Moderate OA)	53.30%	46.70%	46.70%	0.873
Bilateral Involvement	96.70%	100%	100%	0.358

PRP Preparation and administration: A standardized double-spin centrifugation technique was used to produce leukocyte-poor PRP. The final product contained over 1,000,000platelets/µL. All injections were performed under aseptic conditions using a supero-lateral approach.

Figure 1: PRP prepared using A double-spin centrifuge protocol to concentrate platelets in which first the blood withdrawn was centrifuged at 3000 rpm for 10 minutes followed by a speed of 1500 rpm for same time.

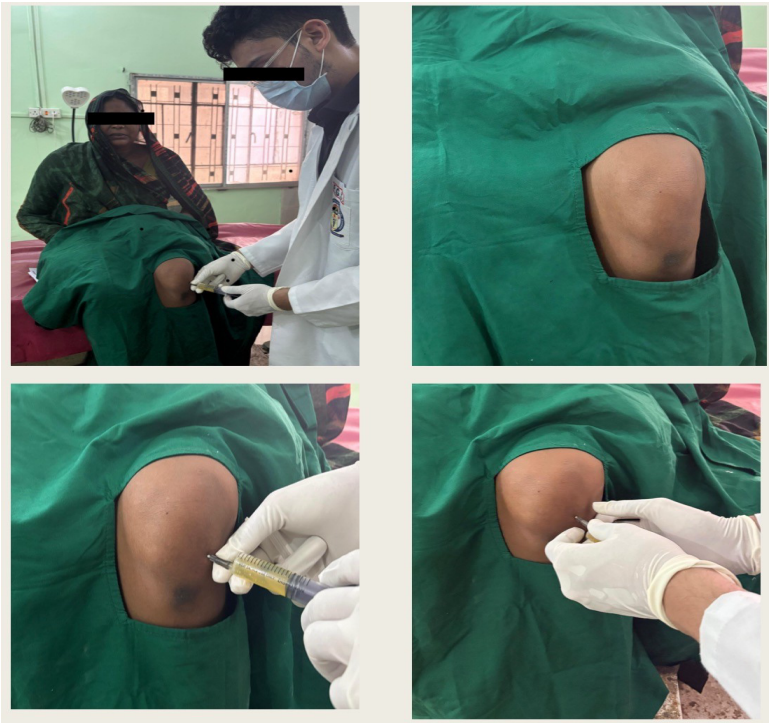

Figure 2: Intra-articular administration of autologous PRP using a supero-lateral approach under aseptic conditions.

Study Design

Patients were systematically allocated into three groups (n = 30 each):

1. **Group A:** Single PRP injection at day zero.
2. **Group B:** Two injections (Day 0 and Week 2).
3. **Group C:** Three injections (Day 0, Week 2, and Week 4).

Assessment Protocol

Evaluations occurred at baseline, 6 weeks,12 weeks, and 6 months.

- **VAS (Visual Analog Scale):** A 0–10 scale for pain intensity.
- **WOMAC Index:** A 24-item questionnaire covering pain, stiffness, and physical function.
- **Safety:** Monitoring for adverse events like swelling or localized pain.

Results

1. Pain Assessment (VAS Scores)

The study achieved a 100% follow-up rate with all 90patients completing the 6-month assessment period.

- **Baseline Comparison:** At the start of the study, Visual Analog Scale (VAS) scores were comparable across all groups (Single: 7.3±0.7, Double: 7.3±0.8, Triple: 7.6±0.7), indicating homogeneous symptom severity.
- **6-WeekProgress:** All groups showed significant pain reduction from baseline ($p<0.001$).
- **12-Week Peak:** Every treatment group reached its peak therapeutic benefit at 12 weeks, with scores dropping to 4.3±1.2 for the single dose, 3.8±1.0 for the double-dose, and 3.2±1.3 for the triple-dose groups.
- **6-Month Divergence:** At the final follow-up, the single and double- dose groups experienced partial deterioration (scores rising to 5.3±1.2 and 5.1±0.9). In contrast, the triple-dose group maintained sustained benefits with a final VAS score of 3.0±0.7.
- **Overall Improvement:** The triple-dose regimen achieved a 60.5% improvement from baseline, significantly outperforming the single (27.4%) and double-dose (30.1%) groups.

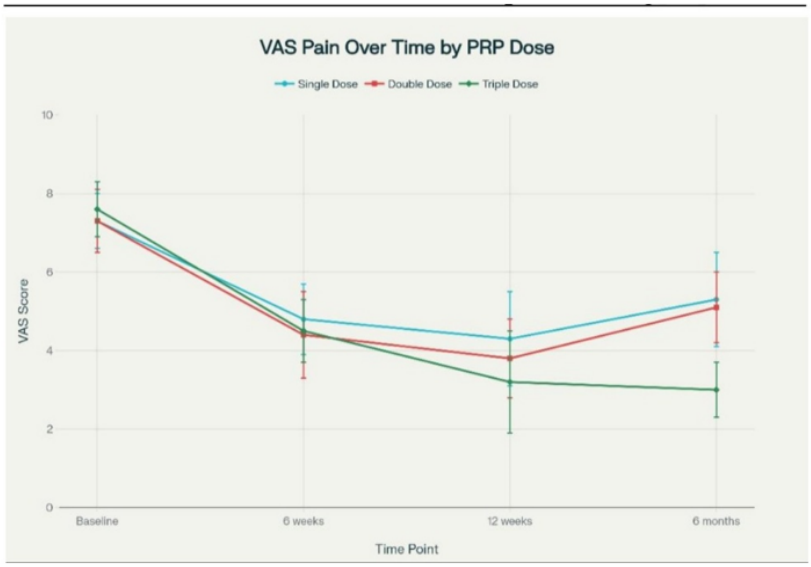

Figure 3: Graph comparing VAS scores at Y-axis and different time points at X-axis, blue line indicating journey of group A patients, red indicating that of group B whereas green indicating group C patients. A significant reduction VAS scores is noted at 6 months' time point in group C patients who were given 3 doses of PRP. Whereas group A and group B experienced deterioration in 6 month follow-up

2. Functional Evaluation (WOMAC Scores)

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) mirrored the pain trends observed in the VAS scores.

- **Baseline Scores:** Baseline points were recorded as 65.0 for Group A, 67.0 for Group B, and 66.5 for Group C.
- **Improvement Trends:** All groups demonstrated substantial initial functional improvement by 6 weeks and reached peak improvement at 12 weeks.
- **Sustainability:** Similar to pain scores, only the triple-dose group maintained sustained functional improvement at 6 months, while the other two groups showed partial deterioration from their peak.

Table 2: shows WOMAC scores of single dose, double dose and triple dose patient groups at baseline, 6 weeks, 12 weeks and 6 month time points

Timepoint	Single Dose	Double Dose	Triple Dose
Baseline	65	67	66.5
6 weeks	46.7	45.9	40.2
12 weeks	44	42.7	36.3
6 months	48.6	49.3	38.5

Figure 4: Graph comparing WOMAC scores at Y-axis and different time points at X-axis, blue line indicating journey of group A patients, red indicating that of group B whereas green indicating group C patients. A significant reduction of WOMAC scores is noted at 6 months time point in group C patients who were given 3 doses of PRP. Whereas group A and group B experienced deterioration in 6 month follow-up

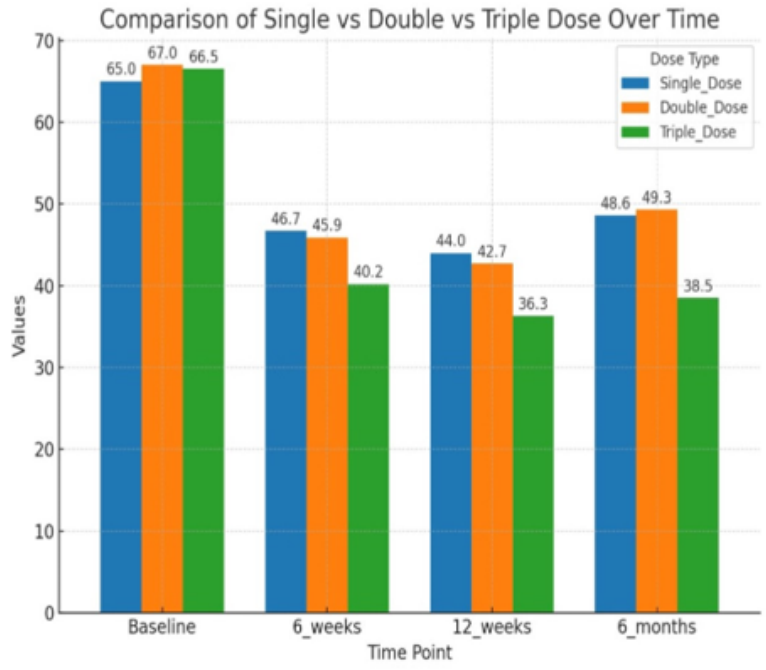

Figure 5: A bar graph comparing WOMAC score of group A, group B, group C at baseline, 6 weeks, 12 weeks and 6 months time point.

3. Safety Profile and Adverse Events

The safety profile was excellent across all groups, with no serious adverse events, infections, or allergic reactions reported.

- **Injection Site Pain:** Mild, self-limiting pain was reported by 16.7% of the single-dose group, 20.0% of the double-dose group, and 23.3% of the triple-dose group. This typically resolved within 48–72 hours.
- **Transient Swelling:** Knee swelling occurred in 10.0%, 13.3% and 16.7% of patients in the single, double, and triple-dose groups, respectively.
- **Patient Satisfaction:** Satisfaction scores remained high (>85%) across all cohorts, regardless of minor transient reactions.

Clinical Outcome Trends (VAS& WOMAC): This table details the progression from baseline to the 6-month follow- up, highlighting the superior performance of the triple-dose regimen.

Table 3: Clinical Outcome Trends (VAS& WOMAC)

Finding	Single Dose	Double Dose	Triple Dose	Significance (at 6 mo)
VAS Baseline	7.3 ± 0.7	7.3 ± 0.8	7.6 ± 0.7	p = 0.742
VAS 6 Months	5.3 ± 1.2	5.1 ± 0.9	3.0 ± 0.7	p < 0.001
VAS % Improvement	27.40%	30.10%	60.50%	Superior
WOMAC Baseline (Function)	65	67	66.5	Comparable
WOMAC 6 Months (Function)	48.6	49.3	38.5	p < 0.001
WOMAC % Improvement	24.50%	27.50%	42.70%	Superior

Table 4: Safety and Adverse Events Profile

Adverse Event	Single Dose (%)	Double Dose (%)	Triple Dose (%)	Resolution
Injection Site Pain	16.70%	20.00%	23.30%	48–72 Hours
Transient Swelling	10.00%	13.30%	16.70%	Spontaneous
Infection	0.00%	0.00%	0.00%	N/A
Allergic Reactions	0.00%	0.00%	0.00%	N/A
Patient Satisfaction	>85%	>85%	>85%	High

While more injections led to a slightly higher frequency of minor reactions, all events were self-limiting and did not affect the overall safety profile.

Study Limitations and Future Research: While the results are significant, several limitations should be considered when interpreting the data:

- **Follow-up Duration:** The 6-month follow-up period may not capture the full long-term course of PRP effects or the duration of its disease-modifying potential.
- **Disease Severity:** The study was limited to patients with early to moderate OA (KL Grades I-II). Consequently, the results may not be generalized to patients with advanced (KL Grade III-IV) joint degeneration.
- **Lack of Placebo Control:** As there was no saline/placebo control group, the improvements could theoretically be influenced by non-specific effects of repeated joint injections. However, the significant divergence in outcomes between the groups suggests a true therapeutic effect.
- **Standardization Challenges:** Variations in PRP preparation, such as centrifugation protocols and leukocyte content, remain an ongoing challenge in the field that can influence outcomes across different clinical settings.

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