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Comparative Outcome Analysis of Leukocyte-Rich Platelet-rich Plasma, Leukocyte-Poor Platelet-rich Plasma, Injectable Platelet-rich Fibrin and Corticosteroid Injections in Periarthritis of the Shoulder: A Double-Blinded, Four-Arm Randomized Controlled Trial

Aadithya Siddarth Sridhar[1,2], Naveen Jeyaraman[2,3], Arunagiri Gunasekar[2], Sanjeevi Bharadwaj[4], Arulkumar Nallakumarasamy[2,5], Madhan Jeyaraman[2,3]

Learning Point of the Article:

Injectable platelet-rich fibrin and leukocyte-poor platelet-rich plasma provide superior and sustained pain relief and functional improvement compared to corticosteroid injections in periarthritis of the shoulder, making them safe and durable regenerative alternatives for long-term management.

Abstract

Introduction: Periarthritis of the shoulder (adhesive capsulitis) is a common, disabling condition. Autologous platelet concentrates have emerged as regenerative alternatives to corticosteroids. Still, the comparative efficacy of leukocyte-rich platelet-rich plasma (LR-PRP), leukocyte-poor platelet-rich plasma (LP-PRP), injectable platelet-rich fibrin (iPRF), and triamcinolone remains undefined.

Objective: This study aimed to compare the efficacy, safety, and functional outcome of intra-articular LR-PRP, LP-PRP, iPRF, and triamcinolone in patients with periarthritis of the shoulder over 12 months.

Materials and Methods: In this single-center, double-blinded, four-arm randomized controlled trial, 64 patients were allocated 1:1:1:1 (n = 16 per arm) to receive a single intra-articular injection of 5–6 mL LR-PRP, 5–6 mL LP-PRP, 5–6 mL iPRF, or 1 mL (40 mg) triamcinolone. The primary outcomes were the Visual Analog Scale (VAS) for pain and the disabilities of the Arm, Shoulder and Hand (DASH) score, assessed at baseline and at 1, 3, 6, and 12 months. Data were analyzed using repeated-measures analysis of variance in Statistical Package for the Social Sciences v26.0, with $P < 0.05$ considered significant.

Results: All groups improved significantly from baseline ($P < 0.001$). At 1 month, the triamcinolone group showed the greatest improvement (VAS 3.1; DASH 30.2). From 6 months onward, the platelet-concentrate arms were superior; at 12 months, iPRF achieved the best outcomes (VAS 1.6 ± 0.6; DASH 15.0 ± 4.6), followed by LP-PRP (VAS 1.8; DASH 16.8) and LR-PRP (VAS 2.1; DASH 19.2), whereas the triamcinolone group regressed (VAS 4.2; DASH 37.4) (between-group $P < 0.001$ at 12 months). Adverse events were transient; post-injection swelling and pain were more frequent with LR-PRP.

Conclusion: Corticosteroids offered the fastest early relief, but their effect was not durable. Platelet concentrates, particularly iPRF and LP-PRP, produced superior and sustained pain and functional benefit at 12 months with an excellent safety profile, supporting their use as durable

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Author's Photo Gallery


Dr. Aadithya Siddarth Sridhar


Dr. Naveen Jeyaraman


Dr. Arunagiri Gunasekar


Dr. Sanjeevi Bharadwaj


Dr. Arulkumar Nallakumarasamy


Dr. Madhan Jeyaraman

[1]Department of Orthopaedics, Faculty of Medicine – Sri Lalithambigai Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai, Tamil Nadu, India,
[2]Department of Regenerative Medicine, Agathisha Institute of Stemcell and Regenerative Medicine, Chennai, Tamil Nadu, India,
[3]Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai, Tamil Nadu, India,
[4]Trauma and Orthopaedic Registrar, Wye Valley, National Health Service (NHS) Trust, Hereford, United Kingdom,
[5]Department of Orthopaedics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India.

Address of Correspondence:
Dr. Madhan Jeyaraman,
Department of Orthopaedics, ACS Medical College and Hospital, Dr. MGR Educational and Research Institute, Chennai, Tamil Nadu, India.
E-mail: madhanjeyaraman@gmail.com

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regenerative options for periarthritis of the shoulder.

Keywords: Periarthritis shoulder, adhesive capsulitis, platelet-rich plasma, injectable platelet-rich fibrin, corticosteroids.

Introduction

Adhesive capsulitis or "frozen shoulder" is an inflammatory and fibrotic disease of the glenohumeral joint capsule, which presents with progressive pain, stiffness, and limitation of both active and passive range of motion, especially in external rotation [1]. It is thought to impact 2–5% of the general population and is one of the most common causes of shoulder pain and reduced mobility in clinical practice. The condition is being recognized more and more as a weak nosological diagnosis, and several authors have advocated for the need for more descriptive criteria [2]. It is more common among people aged 40–60 years and is also associated with diabetes mellitus, with people who have diabetes having a much greater risk of developing the disease. Periarthritis is a significant and ever-increasing clinical burden in India and the world at large, where type 2 diabetes is a major burden [3].

Conventional management involves the use of analgesia, physiotherapy, intra-articular corticosteroid injection, hydrodilatation, manipulation under anesthetic and arthroscopic capsular release [4]. The most frequently used intra-articular injection is corticosteroid (usually triamcinolone), which provides rapid pain relief reliably, and good quality trials and reviews have established that it has meaningful short-term benefit, including in patients with diabetes; in diabetic patients, there is also good evidence that it has long-term benefits [5]. Other surgical procedures investigated include hydrodilatation, suprascapular nerve block, bursal injection and optimized steroid doses [6]. However, the advantages of corticosteroids are often temporary, and repeated use is known to have associated risks of cartilage damage, tendon weakening, transient hyperglycemia and hypothalamic–pituitary–adrenal suppression [7].

Autologous platelet concentrates (APCs) – leukocyte-rich platelet-rich plasma (LR-PRP), leukocyte-poor platelet-rich plasma (LP-PRP) and injectable platelet-rich fibrin (iPRF) – have emerged as biologic, steroid-sparing alternatives that deliver the patient's own growth factors to modulate inflammation and promote tissue repair. While there is some existing evidence base with positive results, it is dispersed. In shoulder disorders, randomized trials and meta-analyses have consistently demonstrated both superior and more durable results in pain and function when compared to corticosteroids. Systematic reviews of adhesive capsulitis have demonstrated that platelet-rich plasma (PRP) is as effective as, or superior to, corticosteroid and saline at the longest follow-up with a favorable safety profile [8]. This has been replicated by individual randomized controlled trials (RCTs) in frozen shoulder and periarthritis, and PRP has demonstrated benefits for related shoulder conditions such as rotator cuff tendinopathy. The use of allogeneic PRP as an off-the-shelf option has also been investigated [9]. However, the vast majority of these studies use only one PRP formulation when compared to steroid or hydrodissection, and no study has directly compared leukocyte-rich PRP, leukocyte-poor PRP, and a platelet-rich fibrin (PRF) concentrate in the same blinded PRP protocol [10]. The relative advantage of leukocyte enrichment versus leukocyte depletion and the sustained-release fibrin matrix is therefore unclear, and the clinician is left without evidence to assist in deciding between the biologic options. The present trial was conceived to fill this void specifically [11]. The clinical study compared the efficacy, safety, and functional outcome of intra-articular LR-PRP, LP-PRP, iPRF, and triamcinolone, using VAS and disabilities of the arm, shoulder and hand (DASH) scores as primary endpoints.

Materials and Methods

Study design and setting

A single-center, prospective, double-blinded, 4-arm parallel-group RCT was conducted in the Department of Orthopaedics in the Sri Lalithambigai Medical College and Hospital, Chennai, India. The protocol was approved by the Institutional Ethics Committee (Faculty of Medicine – Sri Lalithambigai Medical College and Hospital, Dr. MGR-ERI/SLMCH/2025/001, dated March 05, 2025) and conducted in accordance with the Declaration of Helsinki and the CONSORT 2010 statement for parallel-group randomized trials. All participants gave informed consent.

Participants

The clinical diagnosis of periarthritis of the shoulder was made, and all consecutive patients who visited the orthopedics outpatient department were screened. Diagnosis should be based on progressive pain, stiffness, and restricted active and passive range of motion (especially external rotation) for at least 4 weeks, without a clear structural shoulder lesion (as determined by radiography and magnetic resonance imaging, when indicated).

Individuals with a shoulder that is stiff and painful and has not improved despite conservative treatment for at least 1 month, with a confirmed diagnosis of adhesive capsulitis, were included in the study. They must be able to provide informed consent,

adhere to the study protocol, and attend regular outpatient follow-up visits as required. Patients with hemoglobin levels below 10 g/dL or platelet counts < 1.0 × 105/μL, those who have received an injection at the treatment site within the past 30 days, or individuals with local infection at the point of injection, systemic infections such as septicemia, or viral conditions including human immunodeficiency virus, hepatitis B, or hepatitis C were excluded from the study. In addition, patients who refuse to comply with the study treatment protocol will be excluded.

Sample size

The sample size was determined based on the clinically important difference in the mean outcome score of 1.02 with a 95% power (80%), with a standard deviation of 1.28 and a two-sided alpha of 0.05 (Z = 1.96). Approximately 16 participants per arm (including dropouts) are required, for a total of 64 participants across 4 arms, using $n = [(Z\alpha/2 + Z\beta) \times \sigma/\Delta]2$. This calculation was carried out based on the principles of sample size estimation and power analysis of clinical research.

Randomization and blinding

Participants were randomly assigned (1:1:1:1) to any of four treatment groups with a random sequence generated on a computer and the order written in sequentially numbered, opaque, sealed envelopes opened only at the time of the injection by a preparing clinician who was not involved in outcome assessment. The participant and the assessor of the outcome were masked (double-blinded). The injectate was made away from the patient and administered in the same syringes to ensure blinding.

Preparation of platelet concentrates

In PRP, the whole venous blood was collected and then processed using differential centrifugation. LR-PRP and LP-PRP were prepared with a double spin protocol: first spin at 2400 rpm for 10 min; second spin at 3600 rpm for 10 min, and the buffy coat was retained for LR-PRP and discarded for LP-PRP to obtain a leukocyte-poor product. Automated platelet counting confirmed platelet yield, and preparations were characterized according to standard platelet-concentrate classification systems. iPRF was prepared by low-speed centrifugation (700 rpm for 3 min) using tubes without any anticoagulants, to yield a liquid fibrin concentrate containing a high concentration of platelets and leukocytes, as well as growth factors released slowly during the preparation process according to the described procedures.

Intervention

On day 0, all participants were injected intra-articularly in their assigned arm, according to Table 1, under strict aseptic conditions. Pre-procedurally, patients were counseled and instructed in active mobilization exercises. Post-procedurally, all arms received the same standardized protocol of rest, ice, compression and elevation (RICE), restriction of movement, progressive exercise program and review.

All arms followed an identical, structured post-injection rehabilitation protocol to avoid co-intervention bias. Phase 1 (day 0–2): relative rest with the RICE regimen, avoidance of strenuous or overhead activity, and paracetamol for analgesia (non-steroidal anti-inflammatory drugs were withheld for the first 48 h to avoid blunting the biologic response). Phase 2 (day 3 to week 2): Gentle pendular (Codman) exercises and pain-limited active-assisted range-of-motion in forward flexion, abduction and rotation, performed 4–6 times daily. Phase 3 (weeks 2–6): Progressive active and passive range-of-motion with pulley, wall-climbing and capsular stretching. Phase 4 (weeks 6–12): Isometric followed by resisted (elastic-band) strengthening of the rotator cuff and periscapular muscles with scapular stabilization drills, progressing to unrestricted functional activity thereafter. Participants attended supervised physiotherapy and were given a mirrored home-exercise program, with adherence checked at each follow-up visit.

Outcome measures

There were two coprimary outcomes: the Visual Analog Scale (VAS) for pain (0–10), and the DASH score (0–100, higher scores representing greater disability), which are both validated for shoulder disorders. Baseline and 1, 3, 6, and 12-month outcomes were measured. Secondary outcomes included the percentage who met the minimal clinically important difference (MCID) using published distribution-based thresholds for shoulder outcome measures and the rate of adverse events.

Table 1: Treatment allocation and intervention protocol across the four study arms (*n* =16 per arm)

Group	Treatment	Volume dose	Description
Group 1	LR-PRP	5–6 mL	Leukocyte-rich PRP, intra-articular, day 0
Group 2	LP-PRP	5–6 mL	Leukocyte-poor PRP, intra-articular, day 0
Group 3	iPRF	5–6 mL	Injectable platelet-rich fibrin, intra-articular, day 0
Group 4	Triamcinolone	1 mL (40 mg)	Corticosteroid control, intra-articular, day 0

LR-PRP: Leucocyte-rich platelet-rich plasma, PRP: Platelet-rich plasma

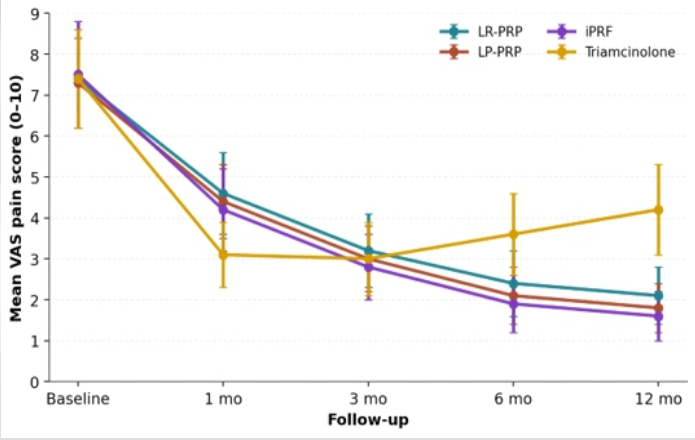

Figure 1: Mean Visual Analog Scale pain scores across follow-up by treatment group.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences v26.0 (IBM Corp., Chicago, IL, USA). Means ± standard deviations are used for continuous variables. Repeated measures analysis of variance (ANOVA) was used to determine within-group change over time, and one-way ANOVA with Bonferroni post hoc to determine between-group differences at each of the time points. Chi-square or Fisher's exact test was used to compare categorical variables. Statistically significant results were obtained for $P < 0.05$ (analysis intention to treat). Pre-specified exploratory subgroup analyses were performed for age (<50 vs. ≥50 years), sex, affected side, and hand dominance by adding a treatment-by-subgroup interaction term to the repeated-measures model.

Results

Baseline characteristics

A total of 64 patients were enrolled, and all reached the 12-month follow-up. The four arms were similar at baseline in terms of age, gender, affected side, duration of symptoms, diabetic status, and baseline VAS score and DASH score (Table 2; all $P > 0.05$), which indicates successful randomization.

Table 2: Baseline demographic and clinical characteristics of the study participants

Characteristics	LR-PRP	LP-PRP	iPRF	Triamcinolone
Number of patients	16	16	16	16
Mean age, years	51.4±8.2	50.8±7.9	52.1±8.6	51.0±8.1
Female, *n* (%)	9 (56)	10 (63)	8 (50)	9 (56)
Dominant shoulder,*n* (%)	7 (44)	8 (50)	7 (44)	8 (50)
Diabetes mellitus, *n* (%)	6 (38)	5 (31)	6 (38)	5 (31)
Symptom duration, months	4.2±1.6	4.0±1.5	4.4±1.7	4.1±1.5
Baseline VAS	7.4±1.2	7.3±1.1	7.5±1.3	7.4±1.2
Baseline DASH	62.5±9.1	61.8±8.9	63.2±9.4	62.1±9.0

LR-PRP: Leukocyte-rich platelet-rich plasma, LP-PRP: Leukocyte-poor platelet-rich plasma, iPRF: Injectable platelet-rich fibrin, VAS: Visual Analog Scale, DASH: Disabilities of the arm, shoulder and hand

Pain outcomes (VAS)

There were highly significant decreases from baseline in VAS in all groups ($P < 0.001$, repeated-measure ANOVA). The triamcinolone arm had the greatest early fall (3.1 ± 0.8) and was better than all platelet groups ($P < 0.05$) at 1 month. The groups merged in 3 months (VAS 2.8–3.2). Shortly after 6 months, there was a clear separation: the platelet concentrate effect kept getting better, whereas the corticosteroid effect was fading. The mean VAS for iPRF was lowest (1.6 ± 0.6), followed by LP-PRP (1.8 ± 0.6) and LR-PRP (2.1 ± 0.7), and highest for triamcinolone (4.2 ± 1.1); iPRF was significantly different from the other groups ($P < 0.001$) (Fig. 1) (Table 3).

Table 3: Mean VAS pain scores (mean±SD) by group across follow-up, with between-group *P*-values (one-way ANOVA)

Group	Baseline	1 month	3 months	6 months	12 months
LR-PRP	7.4±1.2	4.6±1.0	3.2±0.9	2.4±0.8	2.1±0.7
LP-PRP	7.3±1.1	4.4±0.9	3.0±0.8	2.1±0.7	1.8±0.6
iPRF	7.5±1.3	4.2±1.0	2.8±0.8	1.9±0.7	1.6±0.6
Triamcinolone	7.4±1.2	3.1±0.8	3.0±0.9	3.6±1.0	4.2±1.1
P (between groups)	0.94	<0.001	0.62	<0.001	<0.001

LR-PRP: Leukocyte-rich platelet-rich plasma, LP-PRP: Leucocyte-poor platelet-rich plasma, iPRF: Injectable platelet-rich fibrin, VAS: Visual Analog Scale, SD: Standard deviation, ANOVA: Analysis of variance

Functional outcomes (DASH)

The platelet arms showed progressive improvement, whereas triamcinolone showed the highest 1-month functional gain (30.2 ± 6.5), which decreased later on. At 12 months, iPRF achieved the lowest (best) DASH score (15.0 ± 4.6), followed by LP-PRP (16.8 ± 4.9) and LR-PRP (19.2 ± 5.4), all significantly better than triamcinolone (37.4 ± 8.1; $P < 0.001$). The level of improvement in the biologic arms was above the MCID for measures of shoulder disability. Functional trajectories are displayed in Fig. 2. Upon subgroup analysis, the treatment response was consistent across patient characteristics, with no statistically significant interaction between treatment arm and age (<50 vs. ≥50 years), sex, affected side, or hand dominance (dominant vs. non-dominant limb) for either VAS or DASH at 12 months (all interaction $P > 0.05$).

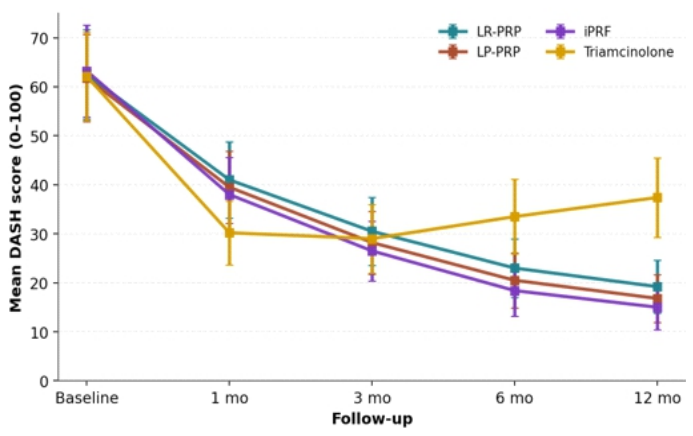

Figure 2: Mean disabilities of the arm, shoulder and hand disability scores (0–100) across follow-up by treatment group. Lower scores indicate better function.

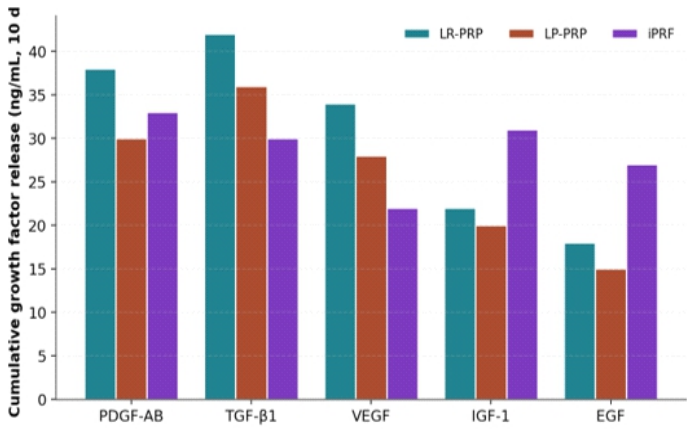

Figure 3: Comparative cumulative growth factor release of leukocyte-rich platelet-rich plasma, leukocyte-poor platelet-rich plasma and injectable platelet-rich fibrin over 10 days.

Growth factor profile

The concentrations prepared showed distinct growth factor signatures as analyzed (Fig. 3). The early release of platelet-derived growth factor (PDGF) and transforming growth factor-beta 1 (TGF-β1) was greatest for LR-PRP, which has a pro-inflammatory leucocyte content, whereas the long-term release of insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF) was greatest for iPRF, due to its slow-release fibrin matrix. This biological gradient is like the superior long-term clinical success seen in the iPRF arm and agrees with the laboratory comparisons of these concentrates.

Safety

There were no serious adverse events, infections or systemic complications noted. The only adverse events were minor, self-limiting swelling and pain, which were most common in the LR-PRP arm and indicative of leucocyte-mediated inflammation. In contrast, LP-PRP and iPRF were better tolerated (Table 4). This safety pattern agrees with comparative leucocyte examination of joint disease. No corticosteroid-associated metabolic events were noted in the study period.

Discussion

A 4-arm double-blinded RCT compared the three platelet concentrates with corticosteroid in periarthritis of the shoulder. The main finding is a reversal in the relative efficacy by 6 and 12 months, with the platelet concentrates (specifically iPRF and LP-PRP) producing better and more lasting pain and functional outcomes than corticosteroids [12]. This is like the prospective randomized open-blind evaluation (PROBE) study by Somisetty et al., in which triamcinolone was found to be superior at 12 weeks, and PRP was superior at 24 weeks, and the meta-analytical evidence that PRP is superior to corticosteroids in terms of longer duration and safety. It also aligns with network and pharmacological reviews of early-stage frozen shoulder [13].

There are clear biological explanations for this disparity. Corticosteroids cause lasting but temporary anti-inflammatory action, but do not treat the underlying capsular fibrosis, and are discontinued as inflammation returns [14]. By contrast, platelet concentrates provide a cascade and synergy of growth factors that stimulate angiogenesis, modulate fibroblasts and organize matrix remodeling and are beneficial over months [15]. The better 12-month results of iPRF may be attributed to the fact that it is an anticoagulant-free fibrin matrix, which extends the release of the growth factors and continues to maintain tissue regeneration [16].

Leukocyte-poor preparations have a biological advantage [17]. Leukocytes provide benefits against microbes. Still, their catabolic and pro-inflammatory mediators may worsen the intra-articular environment, and LR-PRP has been linked to an increase in post-injection swelling and pain [18]. Some good trials, however, report that leukocyte content does not make a significant difference to efficacy or safety, so the question remains up for debate [19]. Our safety data support LP-PRP and iPRF as intra-articular treatments of choice when a reduction in inflammation is desired, and are consistent with

Table 4: Distribution of adverse events by treatment arm over 12 months (*n*=16 per arm)

Adverse event	LR-PRP	LP-PRP	iPRF	Triamcinolone
Transient swelling, *n*	5	2	2	1
Post-injection pain, *n*	4	2	2	3
Infection/serious AE, *n*	0	0	0	0
No adverse event, *n*	7	12	12	12

LR-PRP: Leukocyte-rich platelet-rich plasma, LP-PRP: Leukocyte-poor platelet-rich plasma, iPRF: Injectable platelet-rich fibrin, AE: Adverse event

the inflammatory signal that LR-PRP produces [20].

The three concentrates have unique growth factor profiles that may account for the observed hierarchy of response [21]. LR-PRP containing leukocytes contains high levels of PDGF and TGF-β1 early, but also contains catabolic pro-inflammatory mediators, which can dampen intra-articular benefit and may trigger early flares [22]. LP-PRP carries the anabolic payload of the platelets and reduces this inflammatory burden, and iPRF adds a favorable long-term release of IGF-1 and EGF with a fibrin scaffold, which ensures bioactivity for a prolonged period [23]. The arms iPRF and LP-PRP improve continuously over time, consistent with these profiles, whereas corticosteroid is symptomatically effective but fails to produce long-lasting tissue remodeling [24].

The findings have practical implications. Corticosteroid still has a place, though somewhat limited, when rapid symptom control is critical, such as in the setting of a critical functional demand, or when the patient requires rapid relief, such as before a critical functional demand occurs or when rapid symptom control is of primary importance [25]. A single application of either iPRF or LP-PRP injection is a promising, safe, and cost-effective treatment method, particularly significant for the high incidence of diabetes in the Indian population, where steroid-induced hyperglycemia and chondrotoxicity with repeated doses are a real problem [26]. The platelet concentrates are also autologous and administered as a single injection, which avoids the cumulative risks associated with multiple corticosteroid injections, and are possible within routine orthopedic practice as part of the broader trend toward regenerative orthobiologics [27]. Despite this, they should be adopted in the light of new consensus statements, tiered approaches and regulatory and ethical considerations [28]. The agreement of our findings with other previously completed RCTs and systematic reviews adds to the external validity of the results [29].

Strengths of this study include its prospective double-blinded design, balanced four-arm comparison, complete 12-month follow-up, and use of two validated, complementary outcome measures [30]. The single-center design, relatively small per-arm sample size, which may affect the power for some pairwise comparisons, and lack of objective endpoints for range of motion and imaging are limitations [31]. Further observations of larger multicenter trials, including range of motion, ultrasonographic capsular measurement, and cost-effectiveness analysis, are warranted to confirm and extend these observations [32].

Conclusion

Intra-articular corticosteroid resulted in the quickest early pain reduction, which did not last and was partially reversed after 6 months post-surgery in patients with periarthritis of the shoulder. APCs were more progressive and more enduring, though, with the greatest benefit for VAS pain and DASH function scores at 12 months for injectable PRF and leukocyte-poor PRF, respectively. Leukocyte-poor preparations were also safe and had fewer transient inflammatory adverse events than leukocyte-rich PRP. In contrast, the biologic arms did not have the metabolic and chondrotoxic side effects of repeated corticosteroid use. Intra-articular biologic injection is then a safe, effective, and steroid-sparing option for this common and debilitating condition. For cases where there is a desire for long-term recovery instead of a short-term fix, these approaches (iPRF or LP-PRP) may be recommended over other options. Still, larger multicenter trials with objective range-of-motion endpoints would be required to reinforce these parameters.

Clinical Message

- Corticosteroids provide rapid but short-lived relief – triamcinolone showed the best early improvement at one month, but its effect diminished and even regressed by 12 months.
- Platelet concentrates, especially iPRF and LP-PRP, deliver superior long-term outcomes – both achieved sustained pain reduction and functional improvement at 12 months, outperforming corticosteroids and LR-PRP.
- Safety favors leukocyte-poor biologics – LP-PRP and iPRF were better tolerated with fewer transient inflammatory reactions compared to LR-PRP, making them promising steroid-sparing regenerative options for periarthritis of the shoulder.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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