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High-Dose Platelet-Rich Plasma and Systemic Citrate Exposure: Implications for Calcium Homeostasis and Procedural Safety

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Abstract

Background: Platelet-rich plasma (PRP) has evolved from small-volume orthopaedic use to increasingly high-dose, high-volume protocols across musculoskeletal, spinal, aesthetic, hair restoration, and emerging systemic applications. Efforts to optimise platelet dose have led to larger whole-blood collections and expanded reliance on citrate-based anticoagulants. Although citrate anticoagulation is well established in transfusion and apheresis medicine, its systemic physiological implications have received comparatively limited attention within regenerative practice.

Discussion: Citrate chelates ionised calcium and may acutely reduce the biologically active calcium fraction, particularly when delivery rate exceeds metabolic clearance or when compounded by alkalosis or reduced buffering capacity. In transfusion medicine, citrate-associated hypocalcaemia is anticipated and mitigated through structured procedural safeguards. In contrast, regenerative procedures are often performed outside haematology or apheresis frameworks, and safety protocols may not consistently reflect extracorporeal medicine standards.

Conclusion: Citrate anticoagulation remains appropriate and safe in PRP preparation. However, as platelet dose and systemic exposure increase - particularly with hybrid intravenous or neuroaxial models - predictable electrolyte perturbations warrant structured consideration. Proactive adoption of proportionate safety measures, analogous to apheresis practice, represents a prudent strategy for an evolving field.

Keywords:

Citrate anticoagulation.

Introduction

Platelet-rich plasma (PRP) is now firmly established within regenerative medicine, with applications spanning orthopaedics, sports medicine, dermatology, pulmonary interventions, aesthetics, and spinal procedures Aizawa, H., Kawabata, H., Sato, A., et al. (2020).. Its favourable safety profile is largely attributed to its autologous origin, and consensus reviews consistently describe adverse events as uncommon and typically mild.

Concurrently, the field has moved toward optimisation of platelet dose and total platelet yield, reflecting increasing recognition of dose-dependent biological effects 2. Alves, R., & Grimalt, R. (2018). Achieving higher platelet concentrations frequently requires larger whole-blood processing volumes and, in some protocols, reinjection of additional plasma fractions either locally or intravenously 3. Arita, A., & Tobita, M. (2024). These evolving workflows incrementally increase systemic exposure to processing anticoagulants.

Citrate-based anticoagulants remain the preferred agents for PRP preparation because they preserve platelet integrity and prevent premature activation 4. Berrigan, W. A., Bailowitz, Z., Park, A., et al. (2025).. Citrate has been used safely for over a century in transfusion and apheresis medicine and remains the standard anticoagulant in extracorporeal blood processing 5. Cooper, M. S., & Gittoes, N. J. (2008). Its mechanism, kinetics, and potential complications are well characterised in those settings.

However, a key distinction exists between transfusion medicine and regenerative practice. In apheresis, systemic citrate exposure is anticipated, physiologically monitored, and embedded within structured safety frameworks. In regenerative medicine, systemic citrate exposure is often incidental to the therapeutic objective and is rarely foregrounded in procedural protocols.

As regenerative therapies expand toward higher platelet doses, larger processed blood volumes, and hybrid delivery models that may include systemic plasma reinfusion, the physiological relevance of citrate exposure becomes proportionately greater. Although absolute citrate quantities in PRP workflows are typically lower than those encountered in formal plateletpheresis, the combination of higher-volume processing and systemic delivery narrows the conceptual boundary between small-volume injection therapy and extracorporeal exposure.

To our knowledge, a structured synthesis of citrate physiology applied specifically to high-volume and hybrid PRP workflows has not been previously articulated in the regenerative literature. This manuscript examines citrate-associated calcium dynamics in that context and proposes a proportionate translation of established apheresis safety principles into contemporary high-dose regenerative practice

Citrate Physiology: Lessons from Apheresis Medicine Mechanism of Citrate-Associated Hypocalcaemia

Citrate exerts its anticoagulant effect by reversibly chelating ionised calcium (Ca^{2+}), a necessary cofactor in multiple steps of the coagulation cascade . D'souza, R. S., Her, Y. F., Hussain, N., Karri, J., et al. (2024).. A reduction in circulating ionised calcium may manifest clinically as perioral or digital paraesthesia, carpopedal spasm, and generalized neuromuscular irritability, with progression in more severe cases to sustained tetany. Autonomic features such as tachycardia and diaphoresis may accompany neuromuscular symptoms, and cardiac arrhythmias have been reported in rare instances. In severe and untreated cases, profound hypocalcaemia may precipitate life-threatening cardiac instability. Importantly, total serum calcium may remain within the normal range while the biologically active ionised fraction falls, underscoring the need to consider ionised calcium when evaluating suspected citrate-related reactions.

Under typical physiological conditions, citrate is rapidly metabolised via the tricarboxylic acid (TCA) cycle, with primary clearance occurring in the liver and additional metabolism in skeletal muscle and kidney. This metabolic process regenerates bicarbonate and allows restoration of ionised calcium homeostasis. Clinically significant symptoms arise when the rate of systemic citrate delivery temporarily exceeds metabolic clearance capacity, or when concomitant factors further reduce the ionised calcium fraction 7. Dhurat, R., & Sukesh, M. (2014).

What Apheresis Practice Already Does

In plateletpheresis and plasmapheresis, systemic citrate exposure is anticipated as an inherent component of the procedure and is managed within a structured physiological framework. Donors undergo screening to identify conditions that may predispose to hypocalcaemia or impaired citrate metabolism, and anticoagulant infusion parameters are controlled to limit the rate-dependent decline in ionised calcium. Throughout the procedure, individuals are actively monitored for early manifestations of citrate effect, including perioral paraesthesia, digital tingling, and evolving neuromuscular irritability. Oral or intravenous calcium supplementation is readily available when indicated, and staff are trained to recognise and promptly manage symptomatic hypocalcaemia.

Notably, reported systemic citrate reinfusion volumes during routine plasmapheresis frequently exceed those encountered in most regenerative PRP protocols. Despite these higher exposures, severe reactions remain uncommon in apheresis settings, largely because citrate physiology is anticipated and procedural safeguards are consistently applied. The relative safety of these procedures reflects structured monitoring and preparedness rather than negligible citrate exposure

Why Regenerative Medicine Is Different.

High-dose PRP and hybrid regenerative protocols - including intravenous plasma components, systemic adjunctive delivery, and neuroaxial applications - are increasingly performed by clinicians whose primary training lies in orthopaedics, radiology, sports medicine, pain medicine, dermatology, and aesthetic practice. These disciplines bring substantial expertise in procedural technique, image-guided intervention, and tissue-level biology. However, the systemic physiology of citrate exposure and calcium homeostasis has traditionally been more central to transfusion and apheresis medicine than to these procedural specialties.

As regenerative workflows evolve toward larger processed blood volumes, higher absolute platelet doses, multi-compartment delivery strategies, and the incorporation of intravenous plasma components, systemic citrate exposure becomes incrementally more relevant from a physiological standpoint. Although absolute citrate doses in PRP preparation remain modest compared with formal plateletpheresis or plasmapheresis procedures, the combination of higher-volume processing and hybrid delivery approaches narrows the conceptual distinction between regenerative practice and small-volume extracorporeal exposure. In this context, familiarity with citrate kinetics, ionised calcium dynamics, and symptom recognition becomes proportionately important.

The field is not unsafe. It is simply younger than transfusion medicine in its safety framework maturation.

Risk Amplifiers in Regenerative Settings

Revised Risk Amplifiers in Regenerative Settings

Although citrate exposure during high-dose PRP preparation is generally lower than that encountered in formal plateletpheresis or plasmapheresis, tolerance to citrate is not determined by absolute dose alone. The clinical expression of citrate-associated hypocalcaemia reflects the interaction between citrate load, delivery rate, metabolic clearance capacity, and factors influencing the ionised calcium fraction.

Several contextual variables may influence susceptibility:

Fasting and Metabolic State

Citrate is metabolised primarily through hepatic mitochondrial pathways within the tricarboxylic acid (TCA) cycle. In healthy individuals, clearance is typically rapid. However, prolonged fasting or reduced metabolic substrate availability may theoretically diminish buffering capacity during acute citrate delivery. Direct data in PRP populations are limited, but the underlying metabolic principles are well established

Hydration Status

Relative hypovolaemia may reduce effective distribution volume and transiently increase circulating citrate concentration during reinfusion phases. Ensuring adequate hydration is consistent with standard practice in apheresis settings and represents a low-risk precaution.

Respiratory Alkalosis

Hyperventilation increases calcium binding to albumin, thereby reducing the ionised calcium fraction independent of total serum calcium. Even mild alkalosis may amplify neuromuscular symptoms in the setting of citrate exposure. Procedural anxiety and sympathetic activation can therefore potentiate symptom expression without increasing total citrate dose.

Hepatic Function

Because citrate metabolism is predominantly hepatic, significant liver dysfunction may impair clearance and increase susceptibility to symptomatic hypocalcaemia. While this is rarely relevant in routine PRP, known hepatic disease warrants proportionate caution in higher-volume protocols.

Procedural Context

Delivery into highly innervated or neuroaxial compartments may heighten perception of paraesthesia or neuromuscular irritability during transient electrolyte fluctuation. This may lower the clinical threshold for symptom recognition rather than alter systemic physiology.

Individually, these variables are often clinically insignificant. In combination - particularly during higher-volume processing or systemic plasma reinfusion - they may narrow the physiological buffer against citrate exposure and lower the threshold for symptomatic ionised calcium reduction, even when total citrate doses remain within ranges typically regarded as modest.

A Proportionate Safety Framework for High-Dose PRP

As regenerative protocols evolve toward higher whole-blood processing volumes, the systemic implications of citrate exposure become increasingly relevant. In contemporary orthopaedic literature, processing volumes of approximately 60 mL of whole blood are commonly associated with what is described as "high-dose" PRP, delivering mean platelet doses in the range of ~5.5×10^9 platelets per treatment Dhurat, R., & Sukesh, M. (2014).

As protocols expand further to include hybrid intravenous components and neuroaxial applications, the physiological consequences of systemic citrate exposure warrant greater attention. In transfusion and apheresis medicine, citrate-associated hypocalcaemia is anticipated, mechanistically understood, and proactively mitigated through structured procedural safeguards and monitoring frameworks 9. Fernandes, G. C., & Rodeo, S. A. (2025).

A prudent approach for high-volume PRP or hybrid plasma protocols is therefore to adopt baseline safeguards comparable to those used in apheresis practice, with subsequent modification as real-world safety data accumulate.

Pre-Procedure Risk Assessment and Patient Optimisation

As regenerative protocols expand in volume and complexity, appropriate pre-procedure assessment may help mitigate predictable electrolyte-related effects, particularly in high-volume or hybrid delivery models. Hirayama, J., Azuma, H., Fujihara, M., et al. (2007).

Metabolic State - Citrate is metabolised primarily via the tricarboxylic acid (TCA) cycle in the liver, skeletal muscle, and kidney. Although healthy individuals typically clear citrate rapidly, metabolic state may influence tolerance. Consideration should be given to avoiding prolonged fasting prior to large-volume PRP procedures, as reduced metabolic substrate availability may theoretically diminish buffering capacity.

Hydration Status - Maintenance of adequate intravascular volume is standard practice in donor apheresis settings to reduce vasovagal responses and support haemodynamic stability. Ensuring appropriate hydration prior to high-volume PRP or plasma reinfusion is a reasonable precaution.

Hepatic Function - Citrate metabolism is predominantly hepatic. Significant hepatic dysfunction may increase susceptibility to citrate accumulation and functional hypocalcaemia. While routine liver function testing is not required for standard PRP, known liver disease should prompt procedural caution and consideration of modified delivery parameters.

Baseline Electrolyte Assessment (Selected Patients) - In selected individuals undergoing large-volume or hybrid PRP protocols - particularly those with fasting, known metabolic conditions, or high systemic reinfusion volumes - consideration may be given to baseline ionised calcium assessment where feasible. Total serum calcium alone may be misleading, as ionised calcium represents the physiologically active fraction.

Medication Review - A focused pre-procedure medication review should form part of risk stratification in patients undergoing high-volume or hybrid PRP protocols. Particular attention should be paid to medications that may influence calcium homeostasis, electrolyte balance, hepatic metabolism, or autonomic stability. These may include diuretics, calcium channel blockers, agents affecting vitamin D or parathyroid function, chronic corticosteroid therapy, and drugs associated with hepatic impairment. While routine modification of therapy is not required for standard PRP procedures, the presence of medications that could theoretically lower tolerance to transient ionised calcium fluctuations should prompt individualised procedural planning. This consideration aligns with established principles in transfusion and apheresis medicine, where patient-specific physiological and pharmacological factors are routinely incorporated into risk assessment prior to citrate exposure Marraccini, C., Schiroli, D., Mancuso, P., et al. (2023).

Intra-Procedure Safeguards

Controlled Reinfusion Rates - Citrate toxicity is rate-dependent. In apheresis practice, anticoagulant delivery is carefully regulated to minimise abrupt reductions in ionised calcium. Where plasma reinfusion forms part of regenerative workflows, slow and controlled administration should be considered to reduce systemic fluctuation.

Early Symptom Recognition - Perioral paraesthesia, digital tingling, tremor, and carpopedal spasm represent early manifestations of citrate-mediated hypocalcaemia. Clinical teams should be trained to recognise evolving neuromuscular excitability and distinguish it from isolated procedural anxiety.

Recognition of Respiratory Alkalosis as an Amplifier - Respiratory alkalosis increases calcium binding to albumin, further lowering ionised calcium independent of total calcium concentration. Hyperventilation may therefore potentiate neuromuscular symptoms even at modest citrate exposure, underscoring the importance of maintaining patient reassurance and controlled breathing during procedures. Rahman, E., Rao, P., Abu-Farsakh, H. N., et al. (2024).

Post-Procedure Observation

Observation proportional to volume processed - In apheresis practice, donors are routinely monitored after completion of the procedure, with observation periods extending until symptoms resolve and metabolic equilibrium is restored. A similar proportional approach is reasonable in high-volume regenerative protocols.

Immediate availability of intravenous calcium - Intravenous calcium gluconate is standard therapy for moderate to severe symptomatic hypocalcaemia in apheresis settings. Its availability during high-volume PRP procedures represents a minimal but important safety provision.

Trained personnel capable of recognising citrate reactions - Apheresis guidelines emphasise that citrate-related complications are predictable and manageable when staff are appropriately trained. Regenerative environments performing high-dose or hybrid protocols should ensure equivalent competency.

Rationale for a Structured Approach

Reported systemic citrate reinfusion volumes during routine plasmapheresis frequently exceed those encountered in most PRP workflows Sergio Torloni, A., Lumadue, J, et al. (2012).. However, transfusion medicine achieves a low incidence of serious adverse events not because citrate exposure is negligible, but because exposure is anticipated and managed within a structured physiological framework.

Adopting comparable safeguards in high-dose regenerative practice requires minimal additional infrastructure in medically supervised environments. It does not imply that PRP is inherently unsafe. Rather, it reflects a proportionate translation of established extracorporeal safety principles into an evolving therapeutic domain.

Why Start Conservatively?

As regenerative medicine continues to expand into higher-dose orthobiologic protocols, combination biologic strategies, neuroaxial applications, and hybrid systemic approaches, procedural complexity and systemic exposure inevitably increase 14. Sherif, Z., & Sherif, K. (2025).. Although severe citrate-associated reactions remain uncommon, their pathophysiology is well characterised, predictable, and, in most cases, preventable. In this context, initiating high-volume or hybrid protocols within a conservative safety framework is prudent. Establishing an appropriate safety buffer not only enhances patient protection but also supports clinician confidence and preserves the broader credibility of the regenerative field. A structured and precautionary approach permits data-driven refinement over time, allowing safeguards to be rationally de-escalated if low risk is consistently demonstrated. Conversely, attempting to introduce protective measures reactively, following avoidable adverse events, risks both patient harm and erosion of professional trust Singh, A., Chakravarty, S., Sehgal, D., Rust, B, et al. (2024).

Conclusion

Citrate anticoagulation remains a safe and appropriate foundation for high-quality platelet-rich plasma preparation. However, as regenerative medicine advances toward higher platelet doses, larger processed blood volumes, and hybrid delivery models that may include systemic components, the physiological relevance of citrate exposure increases proportionately.

The mechanisms of citrate-associated hypocalcaemia are well characterised, predictable, and routinely managed in transfusion and apheresis medicine. Translating those established safeguards - structured screening, controlled reinfusion rates, active symptom recognition, and readiness for calcium supplementation - into higher-volume regenerative workflows represents a rational and proportionate evolution of practice.

Innovation in biologic therapy need not outpace physiological discipline. Embedding structured citrate safety principles as regenerative protocols scale will help ensure that therapeutic expansion proceeds alongside deliberate risk mitigation, supporting both patient protection and long-term credibility of the field.

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