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Review Article

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Choice of Anticoagulant in Platelet-Rich Plasma (PRP) Preparation: A Review

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Abstract

Platelet-rich plasma (PRP) is largely utilised in regenerative treatment due to the higher concentration of platelets and growth factors. The selection of an anticoagulant during PRP preparation is crucial, as it impacts platelet yield, activation, and clinical efficacy. This review assesses the commonly used anticoagulants – EDTA, sodium citrate, ACD, and heparin - evaluating their mechanisms, effects on PRP quality, and clinical implications. Sodium citrate is the most used anticoagulant due to its reversible calcium chelation while preserving platelet function. ACD offers similar benefits with added stability, while heparin may induce platelet activation, potentially affecting outcomes. The review also highlights the need for standardized protocols to optimize PRP preparation.

Keywords: Platelet-rich plasma, Anticoagulant, ACD, EDTA, Heparin, Sodium Citrate.

1. Introduction

Platelet-rich plasma (PRP) is an autologous blood-derived product obtained through the concentration and separation of whole blood, resulting in a plasma fraction containing platelet levels above baseline values [1]. PRP has emerged as an important area of interest in regenerative medicine due to its high concentration of bioactive molecules that contribute significantly to tissue repair and regeneration. These molecules include various growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), epidermal growth factor (EGF), and epithelial cell growth factors, as well as cytokines including interleukin-1 (IL-1) [2]. Collectively, these mediators play crucial roles in angiogenesis, cell proliferation, extracellular matrix synthesis, and the regulation of inflammatory processes.

PRP has been extensively investigated for its therapeutic potential in musculoskeletal and degenerative disorders. Clinical studies suggest that PRP may facilitate tissue regeneration and improve recovery outcomes in conditions involving bone, muscle, tendon, cartilage, and ligament injuries, as well as joint degeneration [3,4]. Despite its increasing clinical application, the efficacy of PRP remains a subject of debate. Many published studies are limited by small sample sizes, heterogeneous study designs, and inconsistent outcome measures, resulting in variable and sometimes conflicting clinical findings [5].

One of the major factors contributing to this variability is the lack of standardization in PRP preparation and quality assessment procedures [6]. Differences in centrifugation protocols, platelet concentration levels, leukocyte content, activation methods, and particularly the choice of anticoagulant used during blood collection can substantially influence the biological characteristics of PRP. Anticoagulants are essential for preventing premature platelet activation during processing; however, their chemical properties may directly affect platelet yield, platelet viability, growth factor release, and leukocyte contamination, thereby influencing the overall therapeutic effectiveness of PRP preparations [7].

Given the central role of anticoagulants in PRP preparation and the absence of standardized guidelines regarding their optimal selection, a comparative evaluation of commonly used anticoagulants is warranted. Therefore, the objective of this mini-review is to examine the most frequently employed anticoagulants in PRP preparation and to evaluate their effects on platelet recovery, platelet function, growth factor release, and overall PRP quality.

leukocytes, and the quality of PRP. The synthesis of existing evidence will help this review to contribute to the standardization of PRP preparation protocols and faciliate
the use of PRP in the most optimal ways.

2. Methods

The mini-review was performed by searching for the peer-reviewed articles in the PubMed and Scopus databases using a structured literature search. Studies that were published between the years 2010 and 2025 were considered to encompass both the traditional and modern trends in PRP preparation methodologies. The search strategy involved the combination of the following keywords: “platelet-rich plasma”, “anticoagulant”, “sodium citrate”, “acidcitrate dextrose”, “EDTA”, and “heparin”. The studies had to be selected based on the evaluation of the effects of various anticoagulants on PRP properties, such as the platelet yield, platelet activation, leukocyte content, growth factor release, or clinical results. Such investigations as comparative experimental studies, methodological ones, and corresponding clinical reports received a higher priority. Other articles that were not written in English, case reports, conference abstracts, and studies that did not contain adequate methodological description were omitted. The data were extracted based on the kind of anticoagulant, preparation procedure, platelet recovery, and other effects on PRP quality that had been reported.

3. Anticoagulants in PRP Preparation

The major step in PRP preparation is to select the right anticoagulant while maintaining the most favorable plate let morphology, integrity, and functionality [10]. Acid citrate dextrose-A (ACD-A, sodium citrate (SC) (3.8% or 3.2%), heparin, and EDTA are the common anticoaguants used for PRP preparations due to their capacity to avoid clot formation and their documented use for hematological studies, haemostasis, and coagulation tests [8, 10].
The commonly used anticoagulants in PRP prepara tion and their comparative effects on platelet characteris tics are summarized in Table 1.

Table 1. Summary of Anticoagulants Used in Platelet-Rich Plasma (PRP) Preparation

Anticoag-ula nt	Mechanis m of Ac-tion	Effect on Platelet Yield	Platelet Activatio n Status	Impact on Platelet Morpholo gy	Ad-vantages	Limita-tions	Typical Clinical Applica-tion s	Source s
Sodium Cit-rate (3.2–3.8%)	Reversible calcium che-lation inhibit-ing coagulatio n cascade	High (≈70–80%)	Minimal acti-vation during processin g; reversible	Well pre-served	Simple han-dling, costef-fective, re-versible anti-coagulati on	Transient hypocalcemi a; slightly lower yield than EDTA	Orthopedics , sports medi-cine, tendon and ligament repair	[27- 29]
Acid-CitrateDex-trose (ACD-A)	Calcium che-lation with metabolic support via dextrose	High and consiste nt	Very low premature activation	Excellent preservatio n	Superior platelet stabil-ity, prolonged processing time, repro-ducible re-sults	Higher cost; preparation complexity	Regenerativ e medicine, chronic wound heal-ing, tissue engineering	[30, 31]
Heparin	Enhances antithromb in activity; in-hibits throm-bin	Low to mode-rat e	Partial to premature activation	Variable; may impair integrity	Suitable for citrateintoler-ant patients	Risk of prem-ature growth factor release, HIT risk, lower yield	Limited use; select cosmet-ic or experi-menta l set-tings	[32,33]
EDTA	Strong irre-versible calci-um chelation	Very high	Platelet func-tion markedly inhibited	Altered (spherical, less function-al)	High platelet count, homo-geneou s suspension	Impaired platelet func-tion; limited clinical vali-dation	Primarily laboratory research; not recommend ed for routine	[34]

3.1 Sodium Citrate

Sodium citrate is the most used anticoagulant in PRP preparation due to its reversible calcium chelation, which blocks the coagulation cascade [25]. By binding free calcium ions, sodium citrate avoids thrombin generation and platelet aggregation during centrifugation. Studies show that 3.2–3.8% sodium citrate delivers high platelet recovery (up to 80%) with minimal activation [26]. Its reversibility permits platelets to regain function, making it appropriate for applications like tendon repair where active platelets are required [24]. However, too much citrate may cause transient hypocalcemia, which may result in a slightly lower platelet yield compared to EDTA.

3.2 Acid-Citrate-Dextrose (ACD)

ACD, particularly ACD-A, otherwise known as Anticoagulant Citrate Dextrose Solution or Solution A, is another calcium chelator used in PRP preparation. It contains citric acid, sodium citrate, and dextrose, which offer metabolic support to platelets during storage [25]. Due to its effective bonding, ACD leaves the platelets unaffected while keeping the blood from clotting. Research indicates that ACD delivers an equivalent level of platelet concentrations similar to sodium citrate. However, it provides enhanced stability during prolonged storage [26]. Thus, ACD is preferred in tissue engineering protocols that require delayed PRP application. However, its higher cost and complexity may reduce its use in routine clinical settings. Its lower chelating ability preserves platelet functionality, making it appropriate for regenerative applications where platelet activation and growth factor release are important. Since ACD has a lower pH than sodium citrate, it significantly lowers platelet activation with higher platelet recovery. Given the current evidence backed by other practices and FDA approval, ACD-A remains the gold standard of anticoagulants and one of the best preferred anticoagulants for regenerative applications [24-26].

3.3 Heparin

By augmenting antithrombin activity, heparin prevents thrombin. Unlike citrate-based anticoagulants, heparin does not chelate calcium, allowing partial platelet activation during preparation [25]. As activated platelets may prematurely release growth factors, heparin can reduce platelet functionality [26]. Due to the potential of induc ng heparin-induced thrombocytopenia and higher cost, heparin is less commonly used. However, it may be appropriate for patients with citrate sensitivity or in specific conditions where calcium levels remain unaltered. Furthermore, the lower platelet yield and technical preparation challenges may affect its efficiency in clinical settings. In addition to blood-thinning properties, heparin closely binds to all platelets, thereby making the platelet process difficult. Because of the risks of excess blood processing, heparin isn't an ideal anticoagulant for PRP preparation [24-26]. Additionally, heparin can significantly impact platelet quality and quantity in the final PRP. Hence, experts do not recommend the use of heparin for PRP treatments [24-26].

3.4 EDTA

EDTA is a strong calcium chelator and an effective anticoagulant, although the processing stage needs to follow more precise steps compared to ACD-A. However, it is associated with morphological platelet alterations while transforming them into more spherical and potentially less functional forms. EDTA may yield higher platelet counts where the platelet integrity and activation status are often adjusted. Its ability to deliver homogenous PRP suspensions simplifies preparation, potentially improving consistency in clinical outcomes. EDTA's effects may be mitigated by diffusion while reducing potential adverse impacts. However, its inhibition of platelet function via calcium chelation recommends further investigation in animal models to confirm clinical safety. As this study hasn't been replicated on a larger scale, EDTA is still pending approval from the FDA and other regulatory commissions [9].

4. Comparison of Efficacy Among Anticoagulants

While choosing an anticoagulant, most experts avoid EDTA since it may harm the platelet membrane. Instead, ACD or SC is recommended for preserving platelet quality. Most of the commercial kits use SC and ACD, but there is no clarity on the most effective anticoagulant since studies have shown contradictory results regarding the platelet growth factors and recovery rate [8]. Lei et al compared varied anticoagulants and found that ACD-A is superior to SC and heparin in maintaining platelet membrane integrity and preventing inadvertent platelet acti vation during centrifugation. Compared to sodium citrate and heparin, PRP produced on activation using ACDA secreted more transforming growth factor beta 1 (TGF-β1) as well as human marrow stromal cells [11]. ACD-A has a lower pH and lower extracellular calcium ion concentration than SC.

This environment allows for more platelet aggregation prevention [10]. The advanced performance of ACD is attributed to its low citrate and glucose levels, which support platelet energy metabolism and reduce pH-related viability loss during storage [18].

In a comparative study involving anticoagulants for alopecia treatment in males, the platelet concentration was found to be higher in ACD-A samples (310%) when compared to sodium citrate (100%) and EDTA (110%).

Similarly, platelet morphology, including shape and size, as well as the activation model, was more conserved in ACD-A [20]. Furthermore, Kraus et al reported that ACD -A was linked with increased platelet concentration and extreme platelet activation when compared with sodium citrate [19]. However, Amaral et al. found sodium citrate to be the superior anticoagulant in terms of platelet survival and platelet membrane integrity with a higher TGF-β1 release from PRP, as compared to ACD-A [12].

EDTA was also found to affect the platelet membrane and, hence, is not advisable for anticoagulant use [13]. Mussbacher et al. performed a study to assess the degree of platelet activation after blood storage in different anticoagulants for 30 min. No increase in PF4 concentration was visible with ACD-A, indicating no platelet activation. Sodium citrate did not reveal any rise in PF4 concentration, only when the blood was stored at 4°C. This finding shows a slight dominance of ACD-A over sodium citrate in stopping platelet activation [14]. However, all studies found that both ACD-A and sodium citrate are acceptable anticoagulants.

Harrison et al. revealed that ~20% of subjects considered EDTA as a better option compared to citrate or ACD-A for PRP preparation [15]. To date, citrate-based anticoagulants, such as sodium citrate and ACD-A, are considered suitable anticoagulants in regenerative therapy. However, the reason for this option is mainly based on accumulated evidence in transfusion [16]. Additionally, the reason for EDTA exclusion in PRP preparations has not been clearly explained previously. As described in past studies, EDTA significantly swelled and activated the platelets. When it comes to the inhibition of platelet aggregation followed by platelet collection, EDTA is more efficient than ACD-A and sodium citrate [15].

Likewise, Zhang et al. revealed that different anticoagulants caused varied degrees of lysis and spontaneous platelet activation, leading to variations in PRP quality. Compared with heparin and sodium citrate, EDTA could maintain the structural integrity of platelets, reduce their spontaneous activation, and augment the release of PRP growth factors for an extended period, thus ensuring the biomass of PRP [17]. Additionally, Aizawa H et al. demonstrated that EDTA anticoagulation produced the highest platelet counts with no WBC contamination in pure PRP samples [9]. Hence, the preparation of homogenous and well-suspended PRP is much easier with EDTA than with other anticoagulants [15]. Amaral et al. revealed that the number of platelet cells obtained with sodium citrate was 16.3% less compared to the EDTA samples, while the number of platelets in ACD-A samples was 23% less than EDTA and 8% less than sodium citrate. However, mean platelet volume was higher in EDTA samples, which suggests changes in platelet morphology with lesser cell viability [12].

Conversely, Golański et al. revealed that heparin is not used in coagulation studies because it activates platelets in vitro, which interferes with haemostatic parameter assessment [21]. However, heparin is used in whole blood collection for PRP production [22, 23].

5. Conclusion and Perspectives

The clinical use of platelet-rich plasma has extended significantly in various medical fields in recent years, and it has been used in orthopedics, sports medicine, dentistry, dermatology, and wound management. Characterised by the focus of this mini-review, the biological efficacy of PRP is greatly determined by the variables of preparation, with anticoagulant choice being a key but generally overlooked determinant of its effectiveness. The variation in anticoagulant chemistry has a direct effect on platelet yield, platelet activation status, platelet morphology, and consequently, the release of growth factors, which ultimately determine the outcome of therapy.

This is supported by current evidence that ACD-A is effective in maintaining platelet integrity whilst inhibiting premature platelet activation, which facilitates a regulated release of growth factors at the target site. The stability of the plates that it provides even under long-term storage makes it especially important in delayed or staged applications, like chronic wound healing and tissue regeneration procedures. However, unlike EDTA, its good calcium chelation is linked to distorted platelet morphology and decreased functional sensitivity, which restricts its application in regenerative treatment. Sodium citrate seems to be a feasible and useful alternative, particularly in orthopedics/ musculoskeletal scenarios, where platelet functionality and reversible activation are of utmost importance. On the other hand, heparin seems to be the least desirable anticoagulant to use in preparation of PRP since it tends to cause premature platelet activation, reduce platelet recovery, and some forms of safety issues, limiting its application to select application-specific situations.

Despite these understandings, the field has still been characterized by major problems, which pertain to heterogeneity in PRP preparation procedures and a lack of consistency in reporting anticoagulant use. This variability makes cross-study comparisons more difficult and leads to incongruent clinical evidence on the efficacy of PRP. To overcome such shortcomings, there is a need to create standardised preparation protocols that clearly present the type of anticoagulant and its concentration, and handling protocols.

Future studies should work on purposely designed com parative studies that scientifically compare anticoagu lants in various PRP formulations and clinical indications. The major questions that still exist are how the anticoagu lant choice interacts with leukocyte content, centrifuga tion strategies, and activation methods, and how all these factors interact to determine the clinical outcomes. By elucidating these associations, the field will be able to advance to evidence-based standardisation and higher levels of reproducibility. Conclusively, the choice of anti coagulants must be optimized for clinical use, considering the platelet quantity, the quality of its functions, as well as practical factors. We expect that critical conclusions about the existing evidence synthesis in the context of the given review will promote informed decision-making of clini cians and researchers and contribute to the ongoing opti misation and standardisation.

Conflict of Interest

The authors declare no conflict of interest.

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