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REVIEW

Chen et al: PRP and HA in acute ankle sprains

Platelet-rich plasma and hyaluronic acid in the treatment of acute ankle sprains: A review

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ABSTRACT

Ankle sprains are prevalent musculoskeletal injuries commonly encountered in the general population, particularly among athletes. While conventional treatments are widely practiced, regenerative therapies have emerged as potential adjunctive options. This narrative review aims to assess the role of regenerative therapy in the management of acute ankle sprains and evaluate its efficacy through an analysis of the literature. We focused on studies available in PubMed, restricting our search to English-language articles published between January 2005 and December 2024. Our review identified five studies on platelet-rich plasma (PRP) and one on hyaluronic acid (HA). The PRP studies included four clinical trials and one case report. PRP injections demonstrated short-term benefits in pain reduction and functional recovery, particularly when administered early and in multiple doses. However, long-term outcomes were often comparable to standard treatments or placebo. The study on HA indicated consistent and sustained advantages over placebo in alleviating pain, expediting the return to sport, and reducing recurrence rates. Based on the current evidence, PRP and HA may function as adjunctive therapies for acute ankle sprains, especially for short-term symptom relief and functional recovery. Treatment efficacy appears to be influenced by factors such as injection timing, volume, immobilization protocols, and the concurrent use of nonsteroidal anti-inflammatory drugs. Nonetheless, the evidence base remains constrained by small sample sizes, heterogeneous protocols, and a lack of long-term follow-up. Therefore, further high-quality randomized controlled trials are essential to establish standardized protocols and ascertain the long-term efficacy of these regenerative therapies.

Keywords: Ankle injuries, platelet-rich plasma, hyaluronic acid, regenerative medicine, sprains and strains.

INTRODUCTION

Ankle sprain is a common musculoskeletal injury that occurs frequently in the general population, particularly among those involved in sports activities, with approximately 40% of all traumatic ankle injuries occurring during sports [1]. The most frequent mechanism of injury involves a combination of foot inversion and adduction during plantar flexion, which can damage the lateral ankle ligaments, including the anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL), and posterior talofibular ligament (PTFL) [2]. The ATFL is widely regarded as the weakest and most injured ligament in the lateral ankle complex. Biomechanical studies have shown that among all lateral ligaments, the ATFL has the lowest tensile strength and ultimate load to failure [3]. Furthermore, approximately 40% of individuals affected with acute ankle sprain ultimately develop chronic ankle instability (CAI), which may lead to frequent recurrent ankle sprains, avoidance of sports activities, or even early osteoarthritis of the ankle [4, 5]. This underscores the importance of prompt management of acute ankle sprain in preventing long-term sequelae. However, the treatment of established CAI is beyond the scope of this review, which focuses exclusively on regenerative therapies administered in the acute phase of ankle sprain, typically within the first few weeks of injury. Any mention of CAI in this manuscript is limited to contextual background regarding epidemiology and natural history and does not inform our treatment recommendations or conclusions.

Treatment of acute ankle sprain plays an important role in preventing recurrent ankle sprains and CAI [6]. Ankle sprains are commonly classified into three grades based on severity. Grade I involves mild ligament stretching without rupture or instability. Grade II includes partial ligament tears with moderate pain, swelling, and some joint instability. Grade III represents complete ligament rupture, marked by severe pain, swelling, bruising, functional loss, and significant joint instability [7].

Evidence-based clinical guidelines have provided many treatments for acute ankle sprains, including the Rest, Ice, Compression, Elevation (RICE) protocol, non-steroidal anti-inflammatory drugs (NSAIDs), functional treatment, and surgical therapy [1]. NSAIDs are frequently prescribed for pain management in patients with acute ankle sprains. However, their use may impede the natural healing process because the inflammation they suppress plays a crucial role in tissue recovery [8]. Functional support in the form of an ankle brace or tape is often used in the

management of acute ankle sprains and is recommended for 4–6 weeks over immobilization. Among functional support options, ankle braces are most effective [9]. Surgery appears to be more effective in reducing the occurrence of recurrent lateral ankle sprains (LASs), which is crucial because repeated sprains can increase the risk of developing osteoarthritis. While surgery yields good clinical outcomes in cases of both chronic injuries and acute complete lateral ligament ruptures, functional treatment remains the preferred approach because not all patients need surgery [10]. The treatment of ankle sprain depends on the severity of the injury (Grade I, II, and III sprains, as mentioned above). Grade I sprains are typically managed conservatively with the RICE protocol, early mobilization, and functional rehabilitation, including strengthening and proprioceptive exercises. Grade II sprains need a longer period of protected weight bearing, often with the use of a walking boot or brace, alongside controlled range-of-motion exercises and structured physical therapy, to restore function and prevent chronic instability. As for grade III sprains, surgical intervention may be considered in cases of persistent instability, particularly in high-demand athletes. Post-immobilization rehabilitation focuses on restoring strength, proprioception, and joint stability. Across all grades, pain management with NSAIDs is common, and treatment plans should be individualized based on patient activity level and clinical progress [7].

Although evidence-based guidelines provide various treatment options for acute ankle sprains, the role and effectiveness of regenerative therapies remain inadequately defined in clinical practice. Regenerative approaches, particularly platelet-rich plasma (PRP) and hyaluronic acid (HA) injections, have gained increasing clinical interest based on their biological potential to enhance tissue healing. PRP contains concentrated growth factors that may promote ligament repair and modulate inflammation, while HA has been proposed to facilitate tissue healing through its anti-inflammatory properties [10]. However, despite growing clinical use, the evidence base for these interventions in acute ankle sprains remains fragmented and incompletely synthesized. To our knowledge, there is one systematic review that specifically evaluated PRP for acute ankle sprains [11] and highlighted potential benefits while emphasizing substantial heterogeneity in preparation protocols, injection timing, and outcome measures; the study concluded that high-quality evidence and standardized protocols are needed. However, the review focused

exclusively on PRP and did not address other regenerative modalities, such as HA. Importantly, there is no focused narrative synthesis that specifically examines regenerative injection therapies administered in the acute phase (typically within the first few weeks) of injury, systematically identifies key factors influencing treatment efficacy, or provides practical clinical guidance for implementing these therapies in clinical practice. Therefore, this narrative review aims to address these knowledge gaps by: (1) systematically reviewing the available clinical evidence for regenerative injection therapies—specifically PRP and HA—in the acute phase of ankle sprains; (2) identifying factors that may influence treatment efficacy, including injection timing, volume, and concurrent interventions; (3) synthesizing current evidence regarding short-term and long-term clinical outcomes; and (4) providing practical clinical insights to inform decision-making for patients with acute ankle sprains.

MATERIALS AND METHODS

A literature search was conducted in PubMed on December 15, 2024, covering publications from January 2005 to December 2024. Limiting our search to a single database may have introduced selection bias and potentially missed relevant studies indexed in other databases, such as Embase, Web of Science, or Cochrane Library. However, PubMed was selected as it is the most comprehensive database for biomedical literature and is freely accessible, making our search strategy reproducible for other researchers. The search strategies employed were: (1) (platelet-rich plasma[Title/Abstract] OR PRP[Title/Abstract]) AND (ankle sprain[Title/Abstract] OR lateral ankle sprain[Title/Abstract] OR ankle ligament injury[Title/Abstract]); and (2) (hyaluronic acid[Title/Abstract] OR HA[Title/Abstract] OR sodium hyaluronate[Title/Abstract]) AND (ankle sprain[Title/Abstract] OR lateral ankle sprain[Title/Abstract] OR ankle ligament injury[Title/Abstract]). We restricted our search to Title/Abstract fields rather than full-text to maintain search specificity and focus on studies where regenerative therapies for ankle sprains were a primary focus. While this approach may have reduced sensitivity, it ensured that retrieved articles were directly relevant to our research question. No additional filters were applied to the database search. Two independent reviewers (Y-TC and K-TY) screened all titles and abstracts for eligibility in duplicate, with each reviewer working independently and blinded to the other's decisions. Articles deemed potentially relevant by either reviewer underwent full-text assessment, which was also performed independently

and in duplicate. Any disagreements between the reviewers at the title/abstract screening or full-text assessment stage were resolved through discussion, or when necessary, through consultation with a third reviewer (C-YC) to reach consensus.

The inclusion criteria for literature selection were as follows: (1) studies involving patients diagnosed with acute ankle sprain (defined as injury occurring within the past 6 weeks); (2) clinical studies evaluating the efficacy of regenerative therapies, such as PRP or HA, in the treatment of acute ankle sprains; (3) original clinical research articles, including randomized controlled trials, prospective or retrospective studies, and case reports with detailed clinical documentation; (4) studies reporting relevant clinical outcomes, such as pain relief, functional recovery, or other measures of treatment effectiveness; (5) articles published in English; and (6) studies published between January 2005 and December 2024. The exclusion criteria were: (1) studies focusing on CAI or other chronic ankle conditions rather than acute ankle sprains; (2) non-clinical studies, including animal models, in vitro experiments, or basic science research; (3) review articles, systematic reviews, meta-analyses, and expert opinions; (4) studies that did not involve regenerative therapy or did not specifically evaluate treatment effects for acute ankle sprains; (5) articles published in languages other than English; and (6) studies without full-text availability or incomplete data.

Despite significant improvements in translation tools, study inclusion was restricted to English-language publications to ensure consistency and reliability in data extraction and interpretation by minimizing potential misinterpretation of specialized clinical terminology, treatment protocols, or outcome measures. We acknowledge that this language restriction may have excluded potentially relevant studies published in other languages, particularly from regions where regenerative therapies are actively investigated, and represents a limitation of this review.

A total of 15 articles were initially identified through the database search, comprising nine and six articles related to PRP and HA, respectively. After removing duplicates and screening titles and abstracts, 10 articles underwent full-text assessment, of which 4 articles were excluded (2 focused on CAI rather than acute ankle sprains, 1 was a review article, and 1 was a basic science study without clinical outcomes). Finally, six studies comprising five articles on PRP [12-16] (four clinical trials and one case report) and one on HA [17] (a randomized controlled trial) were included in the

narrative review (Table 1). This systematic approach to literature selection, while limited by a single-database search and language restriction, ensured that all included studies were relevant to the research question and met the predefined quality standards for inclusion in this narrative review.

Prp application for the treatment of acute ankle injury

Of the five articles related to PRP, four were clinical trials and one was a case report. Among the four clinical trials, three were randomized and one was not. Zhang et al. [12] conducted a clinical trial to investigate the effects of PRP injections on the clinical outcomes and healing quality of ATFL in patients with grade II LASs. A total of 83 patients with first-time LAS were divided into three groups: a no-injection group, a group that received a single PRP injection within 48 h of injury, and a group that received two PRP injections (one at 48 h and the other at 4 weeks). PRP was administered under ultrasound guidance, and all ankles were immobilized for 2 weeks. Clinical outcomes were assessed using the American Orthopedic Foot and Ankle Society (AOFAS) and visual analog scale (VAS) scores at 2, 6, 8, 24, and 48 weeks. ATFL quality was evaluated using the magnetic resonance imaging (MRI)-based signal-to-noise ratio (SNR) at 8, 24, and 48 weeks. The PRP injection group had better pain relief and functional outcomes compared with the control group, with the two-injection group showing the most significant improvement at 8 weeks. However, at 6 and 12 months, clinical outcomes were similar across all groups. MRI findings indicated improved ATFL healing quality in all groups over time, with the two-injection group showing the best SNR results at the final follow-up. In conclusion, PRP injections provided early symptom relief in patients with LASs, with two injections leading to superior short-term clinical outcomes and ATFL healing. However, the long-term recovery was similar across groups.

Blanco-Rivera et al. [13] conducted a randomized clinical trial to evaluate the clinical effects of PRP therapy in patients with acute grade II LASs treated with rigid immobilization. A total of 21 patients with first-time sprains were included, all of whom received rigid immobilization for 10 days. The experimental group received a PRP injection over the ATFL prior to immobilization. Pain and functional outcomes were assessed using the VAS and AOFAS scores and the Foot and Ankle Disability Index at 3, 5, 8, and 24 weeks. The PRP group showed greater pain reduction and

better functional scores at 8 weeks than the control group. However, at 24 weeks, both groups showed similar clinical outcomes.

Laver et al. [14] conducted a randomized trial to examine the effects of ultrasound-guided PRP injections on the recovery and dynamic stability of elite athletes with syndesmotic (high ankle) sprains involving anteroinferior tibiofibular ligament tears. Sixteen athletes were randomized into a PRP treatment group (n = 8) or control group (n = 8), both of which followed identical rehabilitation and return-to-play (RTP) criteria. Assessments of clinical outcomes and pain levels, along with dynamic ultrasound assessments, were performed at baseline and 6 weeks after injury. The PRP group had a significantly shorter RTP time (40.8 ± 8.9 days) than that of the control group (59.6 ± 12.0 days, p = 0.006). PRP-treated athletes also reported significantly less residual pain, with only one patient (12.5%) experiencing minor discomfort upon returning to activity compared with five patients (62.5%) in the control group. One patient in the control group required syndesmotic reconstruction owing to persistent pain and disability.

Lai et al. [15] described the case of a 39-year-old runner who developed a high-grade LAS with a complete tear of the ATFL. Despite initial treatment with oral analgesics and rest, the patient sought PRP therapy for faster recovery. A single PRP injection was administered under ultrasound guidance, followed by 4 weeks of immobilization using a cast. Ultrasonography at 4 weeks revealed no ligament gapping, and the cast was removed. At 8 weeks, the patient resumed jogging, and ultrasonography confirmed ligament healing. At 6 months, the patient was pain-free and ran daily, and an MRI confirmed complete ATFL healing. This case supports the use of PRP as a promising nonsurgical option for high-grade LAS recovery.

Rowden et al. [16] conducted a prospective, randomized, double-blind, placebo-controlled trial evaluating PRP therapy for severe ankle sprains in an emergency department setting. Of 1156 patients who were screened, 37 met the inclusion criteria and were enrolled. Four patients withdrew before the injection procedure was completed. The remaining 33 patients were randomized to receive either PRP injection (n = 18) or placebo (normal saline, n = 15). All 33 patients completed the study protocol with no loss to follow-up. Both groups received a single injection with 3-day immobilization in a posterior splint. Outcomes were assessed using VAS and

LEFS at days 0, 3, 8, and 30. No statistically significant differences were observed between groups in either pain scores or functional outcomes at any time point, suggesting that PRP did not provide any additional benefit over placebo for acute ankle sprains.

HA application for the treatment of acute ankle injuries

Only one randomized clinical trial conformed to our targets related to HA treatment. Petrella et al. [17] conducted a randomized controlled prospective trial involving 158 competitive athletes with grade I or II acute LASs. Participants were randomly assigned within 48 h of injury to receive either periarticular HA injection (molecular weight 750–1000 kDa, 20 mg, volume 0.7–1.2 ml, administered using anatomical landmarks) plus standard care (the RICE protocol), or placebo injection plus standard care. The HA injections were administered within 48 h of injury and repeated on day 4. Follow-ups were performed on days 30, 90, and 712. Assessments at baseline and on days 4, 8, 30, 90, and 712 included the evaluation of pain on weight-bearing and during a 20-meter walk (measured using a VAS), patient-reported severity of ankle injury, satisfaction with treatment, time to pain-free and disability-free return to sports, recurrence of ankle sprains, missed sports days, and adverse events (AEs). The HA group had significantly lower VAS scores for pain at all follow-ups than those of the placebo group ($p < 0.001$). Pain-free and disability-free return to sports occurred earlier in the HA group (11 ± 8 days) than in the placebo group (17 ± 8 days, $p < 0.05$). At 24 months, the HA group had fewer recurrent ankle sprains (7 vs. 16, $p < 0.05$), fewer missed sports days (21 vs. 41, $p < 0.002$), and higher patient satisfaction at all time points. No serious AEs were reported. Hence, compared with placebo treatment, periarticular HA injections administered using anatomical landmarks were highly effective and well tolerated, leading to reduced pain, faster recovery, fewer recurrent ankle sprains, and fewer missed days from sports, with sustained benefits for up to 24 months.

DISCUSSION

This review focused exclusively on regenerative therapies for acute ankle sprains (defined as injuries within 6 weeks of occurrence). While CAI has been mentioned as a potential long-term complication of inadequately treated acute sprains, and knee osteoarthritis (KOA) studies are discussed later in an analogical context, neither CAI

nor KOA evidence was used to inform our treatment recommendations, which are based exclusively on the six ankle-sprain-specific studies identified in this review. The following discussion and conclusions apply only to the acute phase of ankle sprain management. Additionally, we acknowledge that our 20-year search window (2005–2024) was specifically chosen to capture the seminal Petrella et al.'s [17] study on HA, which remains the only high-quality randomized controlled trial evaluating HA for acute ankle sprains and continues to be highly cited in contemporary literature. Furthermore, we included one case report [15] due to its detailed ultrasound and MRI documentation of ATFL healing following PRP treatment. Given the extremely limited evidence base for regenerative therapies in acute ankle sprains, we believe these inclusions provide valuable clinical insights while maintaining methodological transparency and rigor. The case report was clearly labeled as such in our data presentation, and its evidence level limitations have been appropriately discussed in the context of the overall findings.

Our recent narrative review examined the literature on regenerative interventions for acute ankle sprains that was available on PubMed. Among the six articles reviewed, five were related to PRP and indicated that it may help patients achieve better short-term clinical outcomes, as determined using AOFAS, VAS, and RTP scores [12-15]. However, a randomized clinical trial conducted by Rowden et al. found that PRP did not provide any additional benefits over placebo. In several studies, no significant differences in age or sex were noted between the experimental and control groups [12-16]. A study by Laver et al. [14] differed slightly from the others. The study focused on athletes with high ankle sprains (syndesmotic sprains), including soccer, rugby, and basketball players; judokas; and downhill mountain bikers. The results showed not only a shorter RTP time but also reduced discomfort compared with that experienced by the control group. Petrella et al. [17] also targeted athletes in their study, investigating the effects of HA treatment. Their primary outcomes showed benefits in terms of VAS score reduction. Compared to the general population, athletes often have access to more structured and intensive rehabilitation programs for acute ankle sprains, which may contribute to the positive results seen in athlete-focused studies [18]. Furthermore, PRP and HA therapies may serve as adjuvant treatments for acute ankle sprains, because most studies included additional interventions, such as the RICE protocol and cast immobilization [12].

We also analyzed the number of injections, injection sites, injection volume, volume of whole blood collected, PRP concentration, time elapsed after the sprain before injection, and duration of immobilization to determine whether these factors influenced the results (Table 1). The number of injections varied across studies, with a single injection being administered in some and two in others. The timing of the injections after the sprain also differed, particularly in the studies in which two injections were administered. For example, in the study by Zhang et al. [12], the second injection was administered 4 weeks after the initial injection, whereas in the study by Laver et al. [14], it was administered just 1 week later. Despite these differences, both studies reported symptomatic relief. The whole blood volume was 20–50 ml, and the injected volume was 0.7–6 ml. In the study by Rowden et al. [16], NSAIDs were avoided during the treatment course. However, in the study by Petrella et al. [17], NSAIDs were used as usual, and acetaminophen (500 mg) was used as a rescue medication. Regarding PRP concentration, only Zhang et al. and Laver et al. [12, 14] specified the increases in PRP concentrations, reporting six- and two- to three-fold increases, respectively. In most studies, injections were administered directly into the ligament under ultrasound guidance. However, Blanco-Rivera et al. and Rowden et al. [13, 16] used different approaches, injecting PRP under the lateral malleolus and at the site of maximal tenderness, respectively. Lastly, the duration of immobilization varied across studies, ranging from 3 days to 4 weeks. Notably, in the study by Rowden et al. [16] in which no significant differences in outcomes were reported, the immobilization period was the shortest, just 3 days; this period was significantly shorter than that in other trials [19]. This suggests that shorter immobilization periods may affect the effectiveness of PRP and HA injections.

PRP preparations have become increasingly popular in various medical fields because of their potential to promote tissue repair [20]. The rationale behind PRP therapy is that concentrated platelets, when injected at injury sites, release biologically active factors such as growth factors, cytokines, lysosomes, and adhesion proteins [21]. These factors help initiate the hemostatic cascade, stimulate the synthesis of new connective tissue, and promote revascularization [22]. The main advantages of PRP include its safety, autologous nature (derived from the patient's blood), and versatile preparation techniques, which allow it to be used in a variety of medical applications [20]. Compared to corticosteroids, PRP has a lower risk of

adverse effects, although post-injection pain, swelling, and rare infections remain possible [23]. However, there are no clear regulations regarding the formulation and composition of PRP injections, which leads to significant variations in platelet content, white blood cell counts, red blood cell contamination, and growth factor concentrations [24]. Additionally, medications, such as NSAIDs, can influence the release of the platelet secretome [25]. NSAIDs are frequently used to alleviate pain and inflammation, particularly in musculoskeletal disorders [26]. They function by inhibiting cyclooxygenase (COX) enzymes, thereby modulating the arachidonic acid pathway [27]. Aspirin irreversibly acetylates COX enzymes, leading to permanent inhibition throughout the platelet's lifespan, whereas most non-aspirin NSAIDs (such as ibuprofen and naproxen) are reversible COX inhibitors with transient effects on platelet function [27]. This inhibition prevents placental growth factor signaling [28] and suppresses the production of key cytokines, including platelet-derived growth factor, fibroblast growth factor, vascular endothelial growth factor, and interleukins (IL-1β, IL-6, and IL-8), while increasing tumor necrosis factor-α levels [29]. Given these effects on platelet-derived mediators, NSAIDs were generally avoided or not recommended in the reviewed PRP [12-16] based on concerns that NSAID-mediated suppression of inflammation and platelet function might interfere with the regenerative healing cascade. In contrast, NSAIDs were permitted as part of standard care in the HA trial by Petrella et al. [17], with 500 mg of acetaminophen available as rescue analgesia, reflecting the distinct non-platelet-dependent mechanism of HA. However, limited data are available on the molecular effects of NSAIDs on PRP efficacy in clinical settings. Further research is required to determine whether NSAID avoidance truly enhances PRP outcomes or whether NSAIDs can be safely used with PRP as they are with HA [25].

Based on the content, we developed a hypothesis-generating treatment algorithm for acute ankle sprains (Figure 1). This algorithm is not intended as a clinical practice guideline or standardized treatment recommendation but rather as a synthesis of the heterogeneous protocols used in the limited reviewed studies, intended to guide future research and inform shared decision-making in selected cases. For acute ankle sprains, the first step is determining whether surgery is necessary or conservative treatment is more appropriate. Shared decision-making with patients and respect for their treatment preferences are also important. For patients who choose conservative

treatment, initial acute management, such as the RICE protocol, can be provided. Based on the protocols used in reviewed studies, PRP injections of 1.5–6 mL from 30–50 ml of blood extracts can be administered into the injured ligament under ultrasound guidance from initial to 11 days after injury and again from 1–4 weeks after injury. Unlike PRP, HA is administered periarticularly rather than intra-ligamentously. Similar to Petrella et al.'s study, periarticular HA injections (0.7–1.2 ml; MW 750–1000 kDa; 20 mg) can be given within 48 hours of injury and repeated on day 4. However, these parameters are derived from individual studies with small sample sizes and should be considered exploratory rather than evidence-based recommendations. Notably, while evidence-based guidelines generally recommend functional support over rigid immobilization for acute ankle sprains [1, 10], all studies evaluating regenerative therapies in our review employed immobilization protocols ranging from 3 days to 4 weeks [12-17]. This discrepancy may reflect concerns about protecting the injection site during the early healing phase or simply represent the protocols chosen by individual research teams. Whether functional support could be safely and effectively combined with PRP or HA injections—potentially offering the benefits of both regenerative therapy and early mobilization—remains an important question for future research. The clinical algorithm presented in Figure 1 summarizes the heterogeneous protocols used in the reviewed studies and should be interpreted as a hypothesis-generating framework to inform future research rather than as a standardized treatment recommendation. Clinicians should individualize treatment decisions based on injury severity, patient activity level, available evidence, institutional protocols, and thorough discussion with patients regarding the limited and preliminary nature of the evidence.

Multiple high-quality studies, including meta-analyses, systematic reviews, and randomized controlled trials, have evaluated the efficacy and safety of PRP, HA, and their combination for the treatment of KOA [30-35]. We acknowledge that the pathophysiology of chronic degenerative joint disease differs fundamentally from acute ligamentous injury, and direct extrapolation from KOA to acute ankle sprains is inappropriate. Nevertheless, we briefly discuss KOA literature here solely to illustrate the biological plausibility and safety profile of combination regenerative therapy and not to support clinical recommendations for acute ankle sprains. Studies on KOA have reported superior pain relief and functional improvement with PRP injection

compared with placebo, corticosteroids, and HA alone, without increasing AEs [30]. Moreover, the combination of PRP with HA has shown superior clinical benefits to those of monotherapy, leading to greater pain reduction and improved joint function [31, 32]. These findings suggest that combination therapy may have synergistic potential, though whether this translates to acute ligamentous injury remains unknown. Given the demonstrated benefits of combining PRP and HA in the treatment of KOA, we were interested in exploring whether a similar combination therapy could be effective for acute ankle sprains. However, a thorough search of the available databases revealed no clinical trials specifically investigating the combined use of PRP and HA for this condition. This represents a hypothesis-generating observation and a promising area for future research. Importantly, the discussion of PRP and HA therapy in KOA is included here solely in an analogical context to illustrate the potential of combination regenerative therapy; it does not inform our treatment algorithms or conclusions regarding acute ankle sprains, which are based exclusively on the six ankle-sprain-specific studies [12-17].

The five identified studies on PRP therapy for acute ankle sprains demonstrated heterogeneous preparation protocols and clinical outcomes. PRP is not a uniform product but varies substantially in composition depending on the preparation methods. Established classification systems have been developed to characterize PRP preparations, including the Platelets, Activation, White cells (PAW) classification [36], the DEPA (Dose of injected platelets, Efficacy of the production method, Purity of the PRP, Activation process) classification [37], and the Mishra classification system [38]. These frameworks categorize PRP based on platelet concentration, leukocyte content, activation method, and preparation technique, all of which may influence biological activity and clinical outcomes. Among the studies included in this narrative review, some used leukocyte-rich PRP while others used leukocyte-poor formulations, and activation methods ranged from autologous thrombin to calcium chloride or no activation. This heterogeneity in PRP composition represents a significant limitation in comparing results across studies and may partially explain the variable clinical outcomes observed. Except for its role in the management of acute ankle sprain, the role of PRP therapy in CAI management remains controversial. The discussion of PRP therapy in CAI is outside the scope of the present study. It was included to explore other applications of regenerative therapy and will not be used as

a basis for the possible treatment algorithm or conclusions regarding acute ankle sprain. A retrospective study evaluated the safety and effectiveness of PRP injections in patients with chronic lateral ankle instability [39]. PRP was injected into the injured talofibular ligaments in three sessions at 7-day intervals. Assessment of clinical and functional outcomes by using the Karlsson score, Cumberland Ankle Instability Tool, Good's grading system, patient satisfaction, and return-to-exercise time showed significant improvements in the Cumberland Ankle Instability Tool and Karlsson scores at 3 months ($p < 0.000$). The mean follow-up period was 17.94 ± 3.25 weeks, with no reported AEs, suggesting promising short-term benefits of PRP [39]. Conversely, a randomized controlled trial investigated the effectiveness of leukocyte-rich PRP (LR-PRP) injections in patients who underwent Modified Broström-Gould surgery for chronic lateral ankle instability. Forty patients were randomized into two groups: one group received standard postoperative management plus three ultrasound-guided LR-PRP injections, whereas the control group received only standard postoperative management. Although both groups showed significant improvements in the VAS and AOFAS scores at 6 months ($p < 0.001$), no significant differences were observed between the PRP and control groups in terms of pain relief, function, or range of motion. The study concluded that LR-PRP did not provide additional clinical or functional benefits compared with conventional postoperative management [40]. PRP and HA may be beneficial for CAI. However, addressing the underlying causes of CAI through surgery or other appropriate treatments remains essential [41]. These CAI data are presented solely for contextual purposes and are outside the scope of the present review; they are not used to inform our treatment algorithm or conclusions regarding acute ankle sprains.

This work has several important limitations that must be acknowledged. First, the evidence base is extremely limited, with only five articles on PRP therapy and one on HA therapy meeting our inclusion criteria. This small number of studies precludes meta-analytic synthesis and limits the strength of any conclusions. Second, our search was restricted to a single database (PubMed) and English-language publications, which may have introduced selection bias and excluded relevant studies published in other languages or indexed in other databases. While this approach ensured consistency in data extraction and interpretation of specialized clinical terminology, it represents a significant methodological limitation. Third, all included studies had

small sample sizes (10–50 participants per group), which limits statistical power and generalizability. Fourth, substantial heterogeneity exists across studies in terms of patient populations (general population vs. athletes), injury severity, PRP preparation protocols, HA formulations, injection techniques, concurrent treatments (immobilization duration and NSAID use), and outcome measures. Regarding PRP specifically, the reviewed studies employed varying preparations that differ in platelet concentration, leukocyte content, and activation methods—parameters that can be characterized using established classification systems, such as PAW, DEPA, and Mishra classifications [36-38]. This heterogeneity in PRP composition may substantially influence clinical outcomes, as different PRP formulations have distinct biological properties and inflammatory profiles. This heterogeneity prevents direct comparison and synthesis of results. Fifth, most studies had short follow-up periods (typically 3–6 months), providing no information about long-term efficacy, safety, or prevention of chronic ankle instability. Sixth, only one study was placebo-controlled [16], and it found no benefit of PRP over placebo, raising concerns about potential placebo effects in the uncontrolled studies. Finally, as a narrative review rather than a systematic review, our work lacks the methodological rigor of pre-registered protocols, risk-of-bias assessment tools, and meta-analytic synthesis. These limitations substantially reduce the certainty of evidence and underscore that our findings should be considered preliminary and hypothesis-generating rather than definitive. Our findings align with and extend the only prior systematic review [12] that specifically evaluated PRP for acute ankle sprains. That review concluded that PRP shows potential benefits for short-term pain reduction and functional improvement but emphasized substantial heterogeneity in PRP preparation protocols, limited long-term data, and the need for high-quality randomized controlled trials with standardized protocols. Our narrative review confirms these conclusions and additionally highlights the following: (1) the single placebo-controlled trial [16] found no benefit of PRP, suggesting potential publication bias or placebo effects in uncontrolled studies; (2) the extremely limited evidence for HA (only one RCT [17]), which has received less attention than PRP; (3) the complete absence of studies examining combination PRP and HA therapy for acute ankle sprains, despite promising results in other conditions; and (4) important methodological inconsistencies across studies, including variable immobilization protocols that conflict with evidence-based guidelines recommending functional support. While our

review provides a broader synthesis including both PRP and HA and offers a hypothesis-generating treatment framework, we emphasize the same cautionary conclusions as the prior systematic review: current evidence remains insufficient to support routine clinical use of regenerative therapies for acute ankle sprains outside of research settings or carefully selected cases with thorough patient counseling. Despite these limitations, we conclude that PRP and HA may serve as adjuvant therapies for acute ankle sprains in selected cases, though the evidence base remains limited and preliminary. Further high-quality randomized controlled trials with standardized PRP preparation, injection protocols, and long-term follow-up are essential to establish definitive recommendations.

CONCLUSION

Low-certainty evidence from a limited number of small studies suggests that PRP or HA may offer short-term symptomatic relief as adjuvant therapies for acute ankle sprains, particularly in athletic populations. However, substantial limitations exist, including small sample sizes, heterogeneous protocols, inconsistent outcome measures, and short follow-up periods, and the only placebo-controlled trial found no benefit of PRP over placebo. These limitations preclude definitive conclusions about efficacy or optimal protocols. Robust, standardized, multicenter randomized controlled trials with adequate sample sizes, standardized preparation protocols, validated outcome measures, long-term follow-up (minimum, 12–24 months), and appropriate controls are required before routine clinical adoption. Future research should investigate combination therapies, optimal dosing and timing, cost-effectiveness, and long-term prevention of chronic ankle instability. Until high-quality evidence becomes available, regenerative therapies should be considered investigational and limited to research settings or carefully selected cases with thorough patient counseling.

Conflicts of interest: Authors declare no conflicts of interest.

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REFERENCES

[1] Vuurberg G, Hoorntje A, Wink LM, van der Doelen BFW, van den Bekerom MP, Dekker R, et al. Diagnosis, treatment and prevention of ankle sprains: update of an evidence-based clinical guideline. Br J Sports Med 2018;52(15):956. https://doi.org/10.1136/bjsports-2017-098106.

[2] Petersen W, Rembitzki IV, Koppenburg AG, Ellermann A, Liebau C, Brüggemann GP, et al. Treatment of acute ankle ligament injuries: a systematic review. Arch Orthop Trauma Surg 2013;133(8):1129-41. https://doi.org/10.1007/s00402-013-1742-5.

[3] Fong DT, Ha SC, Mok KM, Chan CW, Chan KM. Kinematics analysis of ankle inversion ligamentous sprain injuries in sports: five cases from televised tennis competitions. Am J Sports Med 2012;40(11):2627-32. https://doi.org/10.1177/0363546512458259.

[4] van Rijn RM, van Os AG, Bernsen RM, Luijsterburg PA, Koes BW, Bierma-Zeinstra SM. What is the clinical course of acute ankle sprains? A systematic literature review. Am J Med 2008;121(4):324-31.e6. https://doi.org/10.1016/j.amjmed.2007.11.018.

[5] Guillo S, Bauer T, Lee JW, Takao M, Kong SW, Stone JW, et al. Consensus in chronic ankle instability: aetiology, assessment, surgical indications and place for arthroscopy. Orthop Traumatol Surg Res 2013;99(8 Suppl):S411-9. https://doi.org/10.1016/j.otsr.2013.10.009.

[6] Doherty C, Bleakley C, Delahunt E, Holden S. Treatment and prevention of acute and recurrent ankle sprain: an overview of systematic reviews with meta-analysis. Br J Sports Med 2017;51(2):113-25. https://doi.org/10.1136/bjsports-2016-096178.

[7] Halabchi F, Hassabi M. Acute ankle sprain in athletes: Clinical aspects and algorithmic approach. World J Orthop 2020;11(12):534-58. https://doi.org/10.5312/wjo.v11.i12.534.

[8] Struijs PA, Kerkhoffs GM. Ankle sprain: the effects of non-steroidal anti-inflammatory drugs. BMJ Clin Evid 2015;2015:1115. PMID: 26218749.

[9] Kemler E, van de Port I, Backx F, van Dijk CN. A systematic review on the treatment of acute ankle sprain: brace versus other functional treatment types. Sports Med 2011;41(3):185-97. https://doi.org/10.2165/11584370-000000000-00000.

[10] Gaddi D, Mosca A, Piatti M, Munegato D, Catalano M, Di Lorenzo G, et al. Acute Ankle Sprain Management: An Umbrella Review of Systematic Reviews. Front Med (Lausanne) 2022;9:868474. https://doi.org/10.3389/fmed.2022.868474.

[11] Banerjee S, Mishra S, Rajnish RK, Yadav SK, Gupta S, Elhence A. Efficacy of Autologous Platelet-Rich Plasma for the Treatment of Ankle Sprain: A Systematic Review of Literature with Limited Meta-Analysis. Indian J Orthop 2025;59(7):910-9. https://doi.org/10.1007/s43465-025-01418-1.

[12] Zhang J, Wang C, Li X, Fu S, Gu W, Shi Z. Platelet-rich plasma, a biomaterial, for the treatment of anterior talofibular ligament in lateral ankle sprain. Front Bioeng Biotechnol 2022;10:1073063. https://doi.org/10.3389/fbioe.2022.1073063.

[13] Blanco-Rivera J, Elizondo-Rodríguez J, Simental-Mendía M, Vilchez-Cavazos F, Peña-Martínez VM, Acosta-Olivo C. Treatment of lateral ankle sprain with platelet-rich plasma: A randomized clinical study. Foot Ankle Surg 2020;26(7):750-4. https://doi.org/10.1016/j.fas.2019.09.004.

[14] Laver L, Carmont MR, McConkey MO, Palmanovich E, Yaacobi E, Mann G, et al. Plasma rich in growth factors (PRGF) as a treatment for high ankle sprain in elite athletes: a randomized control trial. Knee Surg Sports Traumatol Arthrosc 2015;23(11):3383-92. https://doi.org/10.1007/s00167-014-3119-x.

[15] Lai MWW, Sit RWS. Healing of Complete Tear of the Anterior Talofibular Ligament and Early Ankle Stabilization after Autologous Platelet Rich Plasma: a

Case Report and Literature Review. Arch Bone Jt Surg 2018;6(2):146-9. PMID: 29600268.

[16] Rowden A, Dominici P, D'Orazio J, Manur R, Deitch K, Simpson S, et al. Double-blind, Randomized, Placebo-controlled Study Evaluating the Use of Platelet-rich Plasma Therapy (PRP) for Acute Ankle Sprains in the Emergency Department. J Emerg Med 2015;49(4):546-51. https://doi.org/10.1016/j.jemermed.2015.03.021.

[17] Petrella MJ, Cogliano A, Petrella RJ. Original research: long-term efficacy and safety of periarticular hyaluronic acid in acute ankle sprain. Phys Sportsmed 2009;37(1):64-70. https://doi.org/10.3810/psm.2009.04.1684.

[18] Chinn L, Hertel J. Rehabilitation of ankle and foot injuries in athletes. Clin Sports Med 2010;29(1):157-67, table of contents. https://doi.org/10.1016/j.csm.2009.09.006.

[19] Levine OP, Kondapi K, Tjong VK, Gohal C. Postinjection protocols following platelet-rich plasma administration for knee osteoarthritis: A systematic review. PM R 2024;16(9):1023-9. https://doi.org/10.1002/pmrj.13139.

[20] Zhang Z, Liu P, Xue X, Zhang Z, Wang L, Jiang Y, et al. The role of platelet-rich plasma in biomedicine: A comprehensive overview. iScience 2025;28(2):111705. https://doi.org/10.1016/j.isci.2024.111705.

[21] Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020. Int J Mol Sci 2020;21(20):7794. https://doi.org/10.3390/ijms21207794.

[22] Everts PA, Knape JT, Weibrich G, Schönberger JP, Hoffmann J, Overdevest EP, et al. Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol 2006;38(2):174-87. https://doi.org/10.1051/ject/200638174.

[23] Elksniņš-Finogejevs A, Vidal L, Peredistijs A. Intra-articular platelet-rich plasma vs corticosteroids in the treatment of moderate knee osteoarthritis: a single-center prospective randomized controlled study with a 1-year follow up. J Orthop Surg Res 2020;15(1):257. https://doi.org/10.1186/s13018-020-01753-z.

[24] Huang LH, Rau CS, Zeng WH, Lu TH, Wu YC, Chiu YH, et al. A new technique for separating platelet-rich plasma by a copolymer device — without a centrifugation process. Biomed Pharmacother 2022;153:113481. https://doi.org/10.1016/j.biopha.2022.113481.

[25] Frey C, Yeh PC, Jayaram P. Effects of Antiplatelet and Nonsteroidal Anti-inflammatory Medications on Platelet-Rich Plasma: A Systematic Review. Orthop J Sports Med 2020;8(4):2325967120912841. https://doi.org/10.1177/2325967120912841.

[26] Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain management: current perspectives and novel strategies to improve safety. J Manag Care Pharm 2013;19(9 Suppl A):S3-19. https://doi.org/10.18553/jmcp.2013.19.s9.1.

[27] Wang B, Wu L, Chen J, Dong L, Chen C, Wen Z, et al. Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. Signal Transduct Target Ther 2021;6(1):94. https://doi.org/10.1038/s41392-020-00443-w.

[28] Yan M, Wang Z, Qiu Z, Cui Y, Xiang Q. Platelet signaling in immune landscape: comprehensive mechanism and clinical therapy. Biomark Res 2024;12(1):164. https://doi.org/10.1186/s40364-024-00700-y.

[29] Tarnawski AS, Jones MK. Inhibition of angiogenesis by NSAIDs: molecular mechanisms and clinical implications. J Mol Med (Berl) 2003;81(10):627-36. https://doi.org/10.1007/s00109-003-0479-y.

[30] Qiao X, Yan L, Feng Y, Li X, Zhang K, Lv Z, et al. Efficacy and safety of corticosteroids, hyaluronic acid, and PRP and combination therapy for knee osteoarthritis: a systematic review and network meta-analysis. BMC Musculoskelet Disord 2023;24(1):926. https://doi.org/10.1186/s12891-023-06925-6.

[31] Karasavvidis T, Totlis T, Gilat R, Cole BJ. Platelet-Rich Plasma Combined With Hyaluronic Acid Improves Pain and Function Compared With Hyaluronic Acid Alone in Knee Osteoarthritis: A Systematic Review and Meta-analysis. Arthroscopy 2021;37(4):1277-87.e1. https://doi.org/10.1016/j.arthro.2020.11.052.

[32] Zhao J, Huang H, Liang G, Zeng LF, Yang W, Liu J. Effects and safety of the combination of platelet-rich plasma (PRP) and hyaluronic acid (HA) in the treatment of knee osteoarthritis: a systematic review and meta-analysis. BMC Musculoskelet Disord 2020;21(1):224. https://doi.org/10.1186/s12891-020-03262-w.

[33] Papalia R, Zampogna B, Russo F, Torre G, De Salvatore S, Nobile C, et al. The combined use of platelet rich plasma and hyaluronic acid: prospective results for the treatment of knee osteoarthritis. J Biol Regul Homeost Agents 2019;33(2 Suppl. 1):21-8. PMID: 31168999.

[34] Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials. Cartilage 2021;13(1_suppl):364S-75S. https://doi.org/10.1177/1947603520931170.

[35] Fossati C, Randelli FMN, Sciancalepore F, Maglione D, Pasqualotto S, Ambrogi F, et al. Efficacy of intra-articular injection of combined platelet-rich-plasma (PRP) and hyaluronic acid (HA) in knee degenerative joint disease: a prospective, randomized, double-blind clinical trial. Arch Orthop Trauma Surg 2024;144(11):5039-51. https://doi.org/10.1007/s00402-024-05603-z.

[36] DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. Arthroscopy 2012;28(7):998-1009. https://doi.org/10.1016/j.arthro.2012.04.148.

[37] Magalon J, Chateau AL, Bertrand B, Louis ML, Silvestre A, Giraudo L, et al. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. BMJ Open Sport Exerc Med 2016;2(1):e000060. https://doi.org/10.1136/bmjsem-2015-000060.

[38] Mishra A, Harmon K, Woodall J, Vieira A. Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol 2012;13(7):1185-95. https://doi.org/10.2174/138920112800624283.

[39] Medina-Porqueres I, Martin-Garcia P, Sanz-De-Diego S, Reyes-Eldblom M, Moya-Torrecilla F, Mondragon-Cortes R, et al. Platelet-Rich Plasma Injections in

Chronic Lateral Ankle Instability: A Case Series. Biomedicines 2024;12(5):963. https://doi.org/10.3390/biomedicines12050963.

[40] Sabaghzadeh A, Zarei Kurdkandi H, Ebrahimpour A, Biglari F, Jafari Kafiabadi M. Efficacy of Platelet-Rich Plasma for Chronic Lateral Ankle Instability After Modified Broström-Gould surgery: A Randomized, Single-Blinded, Prospective Controlled Trial. Foot Ankle Orthop 2023;8(2):24730114231168633. https://doi.org/10.1177/24730114231168633.

[41] Urits I, Hasegawa M, Orhurhu V, Peck J, Kelly AC, Kaye RJ, et al. Minimally Invasive Treatment of Chronic Ankle Instability: a Comprehensive Review. Curr Pain Headache Rep 2020;24(3):8. https://doi.org/10.1007/s11916-020-0840-7

TABLES AND FIGURES WITH LEGENDS

Table 1. Summary of studies evaluating regenerative therapies for acute ankle sprains

Literature	Method	Indication for injection	Sample size	Injected material	Times of injection	Duration between injection and injury	Injected volume (ml)	Concentration	Immobilization time after injection	Outcome evaluation methods	Results
Zhang et al. [12]	Clinical trial	First time Grade II LAS	83	PRP (intra-ligament)	2	48 hours / 4 weeks	3–4	6 folds	2 weeks	AOFAS and VAS	Early symptom relief
Blanco-Rivera et al. [13]	RCT	First-time Grade II LAS	21	PRP (intra-ligament)	1	Not reported	5	Not reported	10 days	AOFAS and VAS	Early symptoms and functional relief
Laver et al. [14]	RCT	Elite athletes with AITFL tears	16	PRP (intra-ligament)	2	Initial / 7 days	1.5	2–3 folds	Not reported	RTP	Shorter RTP time and less residual pain
Lai and Sit [15]	Case report	LAS with ATFL complete tear	1	PRP (intra-ligament)	1	11 days	3	Not reported	4 weeks	Dynamic ultrasound images and MRI	Sonography and MRI confirmed healing
Rowden et al. [16]	RCT	Severe ankle sprains	37 enrolled, 33	PRP (intra-ligament)	1	Not reported	5-6	Not reported	3 days	VAS and LEFS	No significant difference

			analyzed								
Petrella et al. [17]	Clinical trial	Competitive athletes with Grade I/II ankle sprains	158	HA (Periarticular)	2	Within 48 hours / day 4	0.7–1.2	MW 750–1000 kDa, 20 mg	Dosing per physician protocol	VAS	Reduced pain, faster recovery

Note: ATFL and AITFL are anatomically distinct ligaments. The ATFL is a component of the lateral ligament complex, frequently injured in inversion ankle sprains. In contrast, the AITFL is part of the syndesmotic ligament complex, which stabilizes the distal tibiofibular joint. Abbreviations: PRP: Platelet-rich plasma; AOFAS: American Orthopedic Foot and Ankle Society; VAS: Visual analog scale; RCT: Randomized controlled trial; AITFL: Anterior inferior tibiofibular ligament; ATFL: Anterior talofibular ligament; RTP: Return-to-play; LAS: Lateral ankle sprains; MRI: Magnetic resonance imaging; NSAIDs: Non-steroidal anti-inflammatory drugs; LEFS: Lower Extremity Functional Scale; HA: Hyaluronic acid; MW: Molecular weight; kDa: Kilodalton.

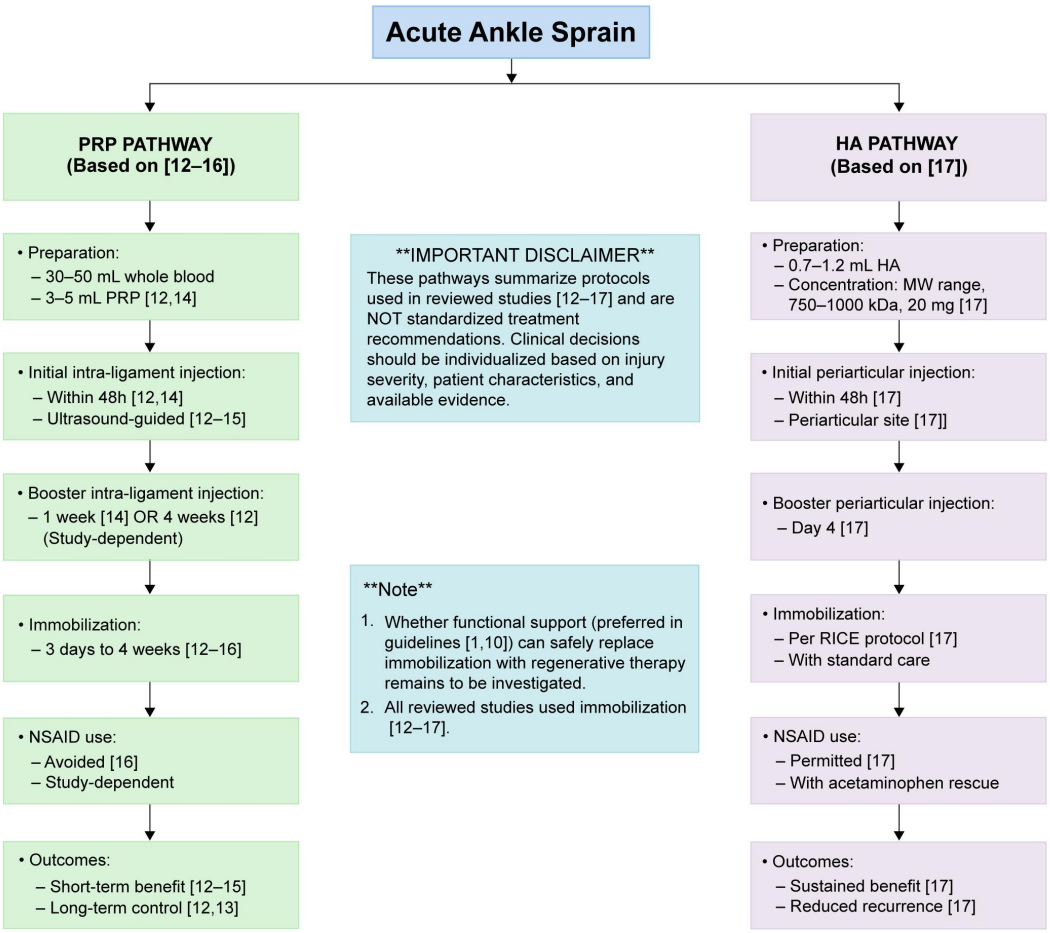

Figure 1. Comparison of PRP and HA injection protocols for acute ankle sprains. This figure summarizes the treatment protocols employed in the reviewed studies for PRP [12-16] and HA [17] injections in cases of acute lateral ankle sprains. The flowchart details preparation methods, injection timing, booster schedules, duration of immobilization, policies regarding NSAIDs, and reported outcomes. It is important to note that these pathways reflect the protocols from the studies and do not constitute standardized treatment recommendations. Clinical decisions should be tailored to individual patient needs. Additionally, while all reviewed studies included immobilization, the safety and efficacy of functional support—recommended in current guidelines [1, 10]—in conjunction with regenerative therapy warrant further investigation. Abbreviations: PRP: Platelet-rich plasma; HA: Hyaluronic acid; NSAID: Non-steroidal anti-inflammatory drug; RICE: Rest, ice, compression, elevation.