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REVIEW

Autologous Peripheral Blood-Derived Orthobiologics for the Management of Elbow Disorders: A Review of Current Clinical Evidence

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ABSTRACT

***Introduction*:** Elbow ailments are common, but conventional treatment modalities have shortcomings, offering only interim pain relief rather than targeting the underlying pathophysiology. The last two decades have seen a marked increase in the use of autologous peripheral blood-derived orthobiologics (APBOs), such as platelet-rich plasma (PRP), to manage elbow disorders. Platelet-rich plasma (PRP) is the most widely used APBO, but its efficacy remains debatable. Consequently, other APBOs, such as platelet lysate (PL), autologous conditioned serum (ACS), gold-induced cytokine (GOLDIC), plasma rich in growth factors (PRGF), autologous protein solution (APS), and hyperacute serum (HS), have been considered. Only a few reviews summarize the results of clinical studies investigating the efficacy of these APBOs in elbow disorders. This review documents the results of clinical studies involving APBOs in managing elbow disorders and summarizes the ongoing clinical studies on different clinical trial protocol repositories comprising these APBOs to manage elbow disorders.

***Methods*:** This systematic review adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines. In December 2024, PubMed, Embase, and Web of Science were accessed with no additional filters or time constraints. All available clinical studies published in English, French, Spanish, German, or Italian concerning the management of elbow disorders by means of APBOs were considered.

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Results: Only three clinical studies met our predefined search and inclusion criteria. In particular, two and one studies involving the use of PL and ACS, respectively, were included in this review. Data from 99 patients were obtained. Of them, 57.6% (57 of 99 patients) were women. The mean length of follow-up was 11.9 ± 0.6 months, and the mean age was 42.0 ± 3.5 years. No complications were reported in any of the studies included. The included studies have low to medium risk of bias, and a very low score on methodological quality. Finally, no clinical studies involving the use of GOLDIC, PRGF, APS or HS were identified, and only one ongoing clinical study involving the use of PL was registered.

Conclusions: The current peer-reviewed published studies demonstrated that administering APBOs, including PL and ACS, might be safe and effective in reducing pain and improving function in patients with elbow disorders. Further, high-quality studies are required.

Keywords: Elbow; Regenerative medicine; Orthobiologics; Autologous peripheral blood-derived orthobiologics; Platelet lysate; Autologous conditioned serum; Gold-induced cytokine; Plasma rich in growth factors; Autologous protein solution; Hyperacute serum

Key Summary Points
Administration of platelet lysate (PL) and autologous conditioned serum (ACS) in patients with lateral epicondylitis is potentially safe and can lead to reduced pain and improved function.
No clinical studies involving the use of gold-induced cytokine (GOLDIC), plasma rich in growth factors (PRGF), autologous protein solution (APS), and hyperacute serum (HS) for managing elbow disorders were identified.
More prospective, sufficiently powered, multi-center, non-randomized and randomized controlled studies with long follow-ups are needed to establish the safety and efficacy of various autologous peripheral blood-derived orthobiologics (APBOs) to manage elbow disorders.
Comparative studies to aid clinicians in determining the ideal APBO for managing elbow disorders are also warranted.

INTRODUCTION

The elbow is essential for upper limb function in daily activities and sports, and enables a range of motions, including flexion, extension, pronation, and supination. The elbow joint consists of the humerus, ulna, and radius. The humeroulnar joint functions as a hinge, allowing flexion and extension, while the humeroradial and proximal radioulnar joints facilitate rotational movements. The stability of the elbow joint is reinforced by the ulnar collateral ligament (UCL), which resists valgus forces; the radial collateral ligament (RCL), which prevents varus forces; and the annular ligament, which secures the radial head, allowing smooth forearm rotation. Major flexor muscles, such as the biceps brachii, brachialis, and brachioradialis, contribute to flexing the elbow and support forearm rotation. Together, these structures allow the complex range of motion and stability of the elbow in various activities [1–3].

Elbow ailments are common [1–3], and encompass a wide range of conditions which might impair essential arm motion and function, negatively affecting the quality of life. Trauma, overuse from repetitive activities, or inflammatory conditions can lead to pain, stiffness, and restricted motor function. Common pathologies include lateral epicondylitis (tennis elbow), cubital tunnel syndrome, olecranon bursitis, medial epicondylitis (golfer's elbow), and fractures [4–16]. Persistent pain may arise from arthritis or tendinopathy, impacting daily function. Joint stiffness, often from trauma, arthritis, or immobilization, limits motion and can cause contractures. Ligament injuries, such as to the

ulnar or radial collateral ligaments, can result in joint instability, making the elbow prone to further injury or dislocation, especially during activities that stress the joint [4–16]. Proper management is essential to prevent these issues.

Conventionally, elbow disorders can be managed conservatively or surgically [17, 18]. Traditional modalities to conservatively manage elbow ailments include physiotherapy, braces, steroid injections, manipulation, and non-steroidal anti-inflammatory drugs (NSAIDs) [19–21]. More recently, orthobiologics have been introduced. Over the last two decades, a significant increase in the use of autologous peripheral blood-derived orthobiologics (APBOs), such as platelet-rich plasma (PRP), for the management of musculoskeletal conditions, has been observed [22–35]. PRP is commonly used: systematic reviews and meta-analyses have shown its efficacy in managing elbow disorders [36–40], though the relevant studies are of moderate to low quality of evidence with a high risk of bias [41–43]. Moreover, the lack of uniform preparation protocols, characterization, and patient variables, including age and comorbidities, further rendered the efficacy of PRP to be disputable [22, 44]. To circumvent the limitations posed by PRP, the use of other APBOs, including platelet lysate (PL), autologous conditioned serum (ACS), gold-induced cytokine (GOLDIC), plasma rich in growth factors (PRGF), autologous protein solution (APS), and hyperacute serum (HS), to manage elbow disorders has been explored [45–50]. The primary aim of this review was to document the results of clinical studies comprising APBOs in the management of elbow disorders. The secondary outcome of interest was to summarize the ongoing clinical investigation on different clinical trial protocol repositories involving these APBOs to manage elbow disorders.

METHODS

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the authors.

Eligibility Criteria

All available clinical studies concerning the management of elbow disorders by means of APBOs were considered. Only studies published in peer-reviewed journals were included. The articles in English, French, Spanish, German, or Italian were eligible, based on authors' language abilities. Only studies categorized as levels I–IV of evidence, as per the 2020 Oxford Centre of Evidence-Based Medicine [51], were taken into consideration. Editorials, letters, reviews, and opinions were excluded. In addition, in vitro experiments, computational studies, animal studies, and cadaveric research, or biomechanical assessments were excluded. Finally, studies with less than 6 months of follow-up were excluded.

Search Strategy

The current systematic review adhered to the guidelines outlined in the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [52]. The following PICOTD algorithm was applied for the literature search:

- Problem: elbow ailments.
- Intervention: ABPOs.
- Comparison: PL, ACS, GOLDIC, PRGF, APS, HS.
- Outcome: VAS, MEPS, complications.
- Timing: minimum of 6 months of follow-up.
- Design: clinical trial.

In December 2024, PubMed, Embase, and Web of Science with no additional filters nor time constraints, were accessed. The following Medical Subject Headings (MeSH) was implemented for the database search: ('platelet lysate' OR 'PL') or ('autologous conditioned serum' OR 'ACS') or ('gold-induced cytokine' OR 'GOLDIC) or ('plasma rich in growth factors' OR 'PRGF') or ('autologous protein solution' or 'APS') or ('hyperacute serum' OR 'HS'

OR 'hypACT') AND ('elbow') or ('tennis elbow' OR 'lateral epicondylitis') or ('golfer's elbow' OR 'medial epicondylitis') or ('pitcher's elbow') or ('ulnar collateral ligament') or ('tendinopathy') or ('bursitis') or ('contusions') or ('cubital tunnel syndrome') or ('dislocation') or ('sprain') or ('fracture') or ('osteoarthritis') or ('osteochondritis') or ('radial tunnel syndrome') or ('repetitive motion disorders').

Selection and Data Collection

Two authors (FM and TB) conducted the search in the aforesaid databases. Manual screening was performed on all retrieved articles, and, if deemed appropriate, their abstracts were accessed. In case of a match, the full text was evaluated. Articles without open-access full texts were also excluded. Additionally, a cross-reference of the bibliographies of full-text articles was performed for potential inclusion. Any disagreements among authors were resolved by the remaining authors (AG and NM), who made the ultimate decision.

Data Items

The data extracted at baseline included author, publication year and journal, follow-up duration, number of patients with related mean age, and number of women. Extraction was performed using Microsoft Office Excel version 16.0 (Microsoft Corporation, Redmond, WA, USA).

Assessment of the Risk of Bias

The risk of bias (RoB) assessment followed the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions [54]. Randomized controlled trials (RCTs) were assessed using the revised RoB assessment tool (RoB2) [55, 56] of the Cochrane tool for assessing the RoB in RCTs [57]. The following endpoints were considered: bias resulting from the randomization process, bias because of deviations from intended interventions, bias because of missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. The RoB in Nonrandomised Studies of Interventions (ROBINS-I) tool [58] was employed to evaluate nonrandomized controlled trials (non-RCTs). The ROBINS-I chart was created using the Robvis Software (Risk-of-bias VISualization, Riskofbias.info, Bristol, UK) [59].

Coleman Methodology Score

The Coleman Methodology Score (CMS), ranging from 0–100, was used to assess the methodological quality of each included study [53]. The scoring system included points for various factors, and a higher score indicated a higher quality of the study and lower risk of confounding biases [53].

RESULTS

Study Selection

Our initial literature search uncovered 329 articles potentially relevant to the search question. A total of 115 duplicates were eliminated and the remaining 214 articles were screened according to their abstracts. One hundred and seventy-two articles did not meet the inclusion criteria; 96 did not match the study type and design requirements, 64 were excluded based on the screening of titles and abstracts, and 12 were excluded due to language limitations. A full-text review was performed on the remaining 42 articles, following which three articles were selected (Fig. 1).

Overview of Studies

Platelet Lysate (PL)

PL is a derivative of PRP, formulated via a double freeze/thaw cycle (freeze at – 80 °C and thaw at 37 °C) [22, 23]. Two studies involving PL for managing elbow disorders met our inclusion criteria (Table 1).

Scudeller et al. [60] in an N of 1, two contemporary arms, open-label, RCT investigated the efficacy of autologous PL compared to 'wait and see' strategy in bilateral elbow pain. Ultrasound

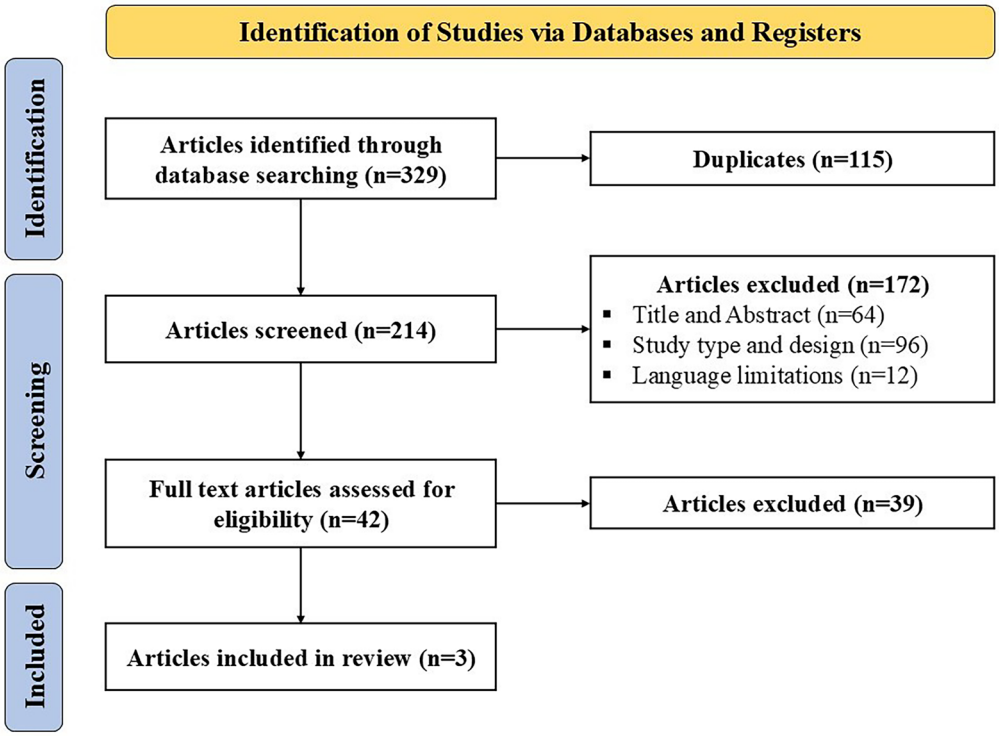

Fig. 1 PRISMA flow chart of the literature search

examination showed bilateral tiny intratendinous calcifications and active inflammation. Magnetic resonance imaging (MRI) showed bilateral thickening of the common extensor tendon along with adjoining soft tissue edema, focal edema areas in the radial head bone and lateral epicondyle of the humerus. 2.5 ml of PL was prepared by freeze-thawing and injected intratendinously three times every fourth week. The main outcome measure was VAS score for pain on elbow extension and resisted wrist extension, evaluated at baseline and at 1-, 3-, and 6-month follow-up. Bilateral pain improvement was reported in both arms at 6-month follow-up compared to the baseline, but the improvement was better in the PL-treated arm compared to the control arm. The shortcomings of this study include a single patient in the study, the patient being a researcher and first author of this study, and lack of statistical significance. Given these limitations, no specific conclusion regarding the efficacy of PL can be made.

Tan et al. [45] retrospectively investigated the safety and efficacy of autologous PL in decreasing pain and increasing function in patients with refractory lateral epicondylitis. The inclusion criteria included patients with a confirmed ultrasonographic diagnosis of lateral epicondylitis, presence of symptoms for at least 3 months, failed conservative treatments, severe lateral elbow pain resisting wrist and forearm extension, persistent pain, and tenderness over the lateral epicondyle. The exclusion criteria included patients with trauma or prior surgery of the elbow, cervical spondylosis, tendon tear, inflammatory arthropathy, rheumatoid disease, previous ulna or radial bone fracture-led joint limitations, osteoporosis, and neurological conditions. PL was formulated via double freeze/thaw cycles. Fifty-six patients met the inclusion criteria, and three weekly doses of 3 ml PL were injected. The outcome measures included PROMs, VAS, and Mayo scores, evaluated at baseline and at 1-, 6-, and 12-month follow-ups. Longitudinal

Table 1 Summary of the main findings of included clinical studies involving platelet lysate for the management of elbow disorders

Author [Reference]	Type of study	Main findings
Scudeller et al. [60]	*N* of 1, two contemporary arm, open-label, randomized controlled clinical trial	Intratendinous injection of PL three times every fourth week in a patient with bilateral elbow pain showed better pain improvement (VAS score) compared to the baseline and control contralateral arm at 6-month follow-up. However, due to a single patient in the study, who is a researcher and first author of this study, no definitive conclusion regarding the effectiveness of PL can be made
Tan et al. [45]	Retrospective study	Administration of three weekly doses of PL in patients with lateral epicondylitis is safe and led to reduced pain (VAS score) and improved function (Mayo score) at 12-month follow-up and reduced inflammation at 1-month follow-up compared to the baseline

PL platelet lysate, *VAS* Visual Analogue Scale

ultrasonography was also performed at baseline and at 1-month follow-up. No adverse events were reported throughout the duration of the study. Statistically significant improvements were observed at all follow-up timepoints compared to the baseline for both VAS and Mayo scores. The color Doppler activity assessed via ultrasonography showed improvement in inflammation at 1-month follow-up compared to the baseline. The shortcomings of this study include retrospective design, short follow-up, small cohort size, and the absence of control group. Administering PL is safe and has been shown to reduce inflammation and pain while improving function in patients with lateral epicondylitis.

Autologous Conditioned Serum (ACS)

ACS is an acellular formulation obtained by incubating the whole blood in a syringe (containing medical-grade glass beads) at 37 °C for 24 h, and subsequent centrifugation of the blood to collect serum [22, 24]. Only one study involving ACS to manage elbow disorders met our inclusion criteria (Table 2).

Ipek et al. [46], in a prospective, non-comparative pilot study, investigated the efficacy of intratendinous injection of ACS in patients with lateral epicondylitis. The inclusion criteria included patients 25–65 years of age, symptoms of lateral epicondylitis for at least 6 months despite using different conservative treatment modalities, such as NSAIDs and injection of steroids. The exclusion criteria included patients with diabetes, rheumatoid arthritis, prior history of fracture or osteoarthritis of the elbow, prior history of surgery for elbow tendinopathy, intra-articular injection of steroids in the last 8 weeks, and physiotherapy in the last 4 weeks. ACS was

Table 2 Summary of the main findings of included clinical studies involving autologous conditioned serum for the management of elbow disorders

Author [Reference]	Type of study	Main findings
Ipek et al. [46]	Prospective, non-comparative pilot study	Administration of four doses of ACS twice a week for 2 weeks in the extensor carpi radialis brevis tendon is safe and resulted in reduced pain (VAS score) and improved function (MEPS and OES) at 3 months and 1-year follow-up compared to the baseline

ACS autologous conditioned serum, *VAS* Visual Analogue Scale, *MEPS* Mayo Elbow Performance Score, *OES* Oxford Elbow Score

formulated using the Orthokine preparation kit (Orthogen, Germany) per the manufacturer's instructions. Forty-two patients met the inclusion criteria and four doses (2 ml, twice a week for 2 weeks) of ACS were administered in the extensor carpi radialis brevis tendon. The outcome measures included PROMs, VAS, MEPS and Oxford Elbow Score (OES), assessed at baseline and at 3-month and 1-year follow-up. No major adverse events were reported throughout the duration of the study. Statistically significant improvements were reported for all PROMs at all follow-up timepoints compared to the baseline. In addition, improvements in all PROMs was statistically significant at 1-year follow-up compared to the 3-month follow-up. The shortcomings of this study include short follow-up, small cohort size, and absence of a control group. Administration of ACS led to significant improvements in pain and function in patients with lateral epicondylitis.

Gold-Induced Cytokine (GOLDIC)

GOLDIC is a type of ACS formulation that involves incubation of the whole blood with the gold particles [22, 25]. To date, there are no published clinical studies involving the use of GOLDIC for the management of different elbow disorders.

Plasma Rich in Growth Factors (PRGF)

PRGF is formulated by activating erythrocyte- and leukocyte-poor PRP with calcium chloride [22]. To date, there are no published clinical studies involving the use of PRGF for the management of different elbow disorders.

Autologous Protein Solution (APS)

APS is formulated by incubating leukocyte-rich PRP with polyacrylamide beads [22]. To date, there are no published clinical studies involving the use of APS for the management of different elbow disorders.

Hyperacute Serum (HS)

HS is formulated by mechanically releasing, via pressing or centrifugation, growth factors and cytokines from the platelet-rich fibrin clot [22, 26]. To date, there are no published clinical studies involving the use of HS for the management of different elbow disorders.

Methodological Quality

The studies by Scudeller et al., Tan et al., and Ipek et al. scored 40, 49, and 49 points on the CMS. All studies scored full points for number of procedures included in each reported outcome, diagnostic certainty, description of procedure

given, outcome criteria and procedure for assessing outcomes, but lost points on study size and mean follow-up.

Risk of Bias Assessment

One of the three (33.3%) included studies was a RCT. The Cochrane ROB 2 was used to evaluate this RCT. The analysis suggested a low risk of bias in the second, third, and fifth domains, while some concerns were posed by the randomization process. In the fourth domain a moderate RoB was identified given the absence of blinding of both the patient and the assessors during the measurement of the outcomes. This article was judged to be at an overall medium risk of bias (Fig. 2).

The ROBINS-I tool was used to assess the RoB in the selected non-RCTs (two out of three included articles). No major concerns were identified with these articles and the only domain found at moderate risk of bias was the sixth, considering the lack of blinding. All the other domains suggested no risk of bias. The ROBINS-I evaluation showed a low overall RoB for the non-RCTs, indicating a satisfactory level of methodological quality (Fig. 3).

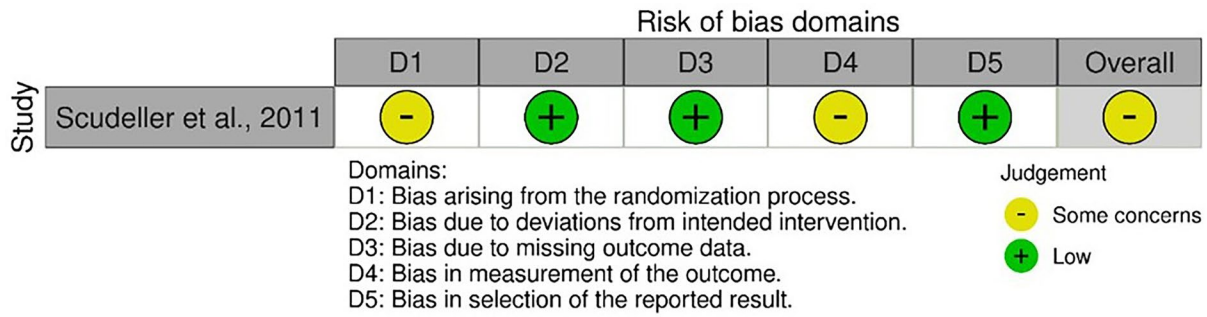

Fig. 2 The RoB2 of the RCT

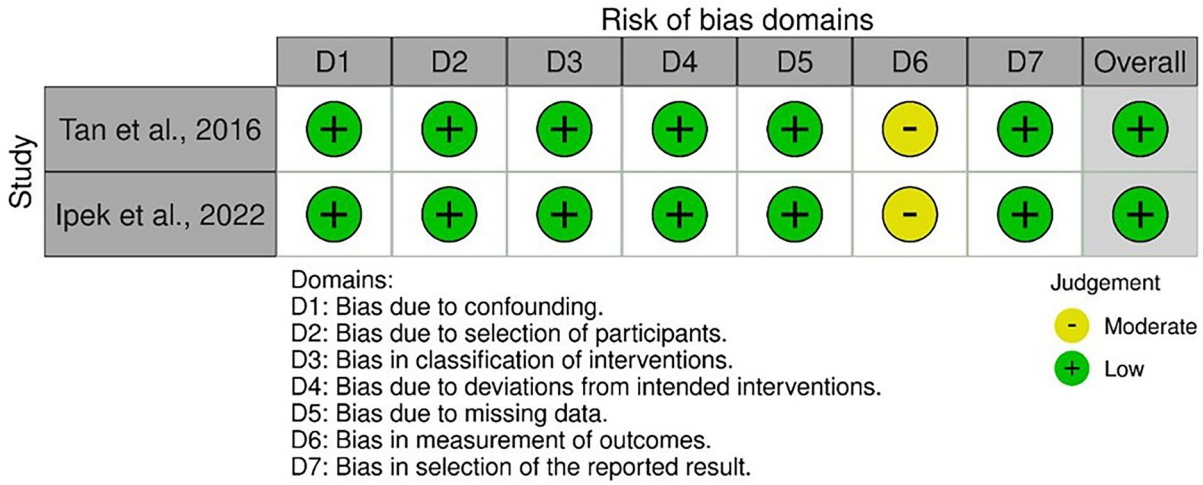

Fig. 3 The ROBINS-I of non-RCTs

Study Characteristics and Results of Individual Studies

Data from 99 patients were retrieved. Of them, 57.6% (57 of 99 patients) were women. The mean follow-up was 11.9 ± 0.6 months, and the mean age was 42.0 ± 3.5 years. Generalities of the included studies are shown in Table 3. No adverse events were reported in any patients.

Ongoing Clinical Trials

As of December 27, 2024, only one clinical trial is listed on ClinicalTrials.gov, CTRI, or ChiCTR to evaluate the safety and/or effectiveness of PL to manage elbow disorders (Table 4).

DISCUSSION

The current systematic review investigated the therapeutic potential of various APBOs, including PL, ACS, GOLDIC, PRGF, APS and HS, to manage elbow disorders. All clinical studies using APBOs to manage various elbow disorders were incorporated. Three studies, based on our inclusion criteria, fulfilled the scope of our manuscript. Specifically, two and one study involving the use of PL and ACS, respectively, were included in this review. No studies evaluating the efficacy and feasibility of GOLDIC, PRGF, APS, and HS in elbow ailments were identified.

Lateral epicondylitis, also known as tennis elbow, is one of the most common causes of elbow pain [61]. Several studies assessed the efficacy of PRP for managing lateral epicondylitis and a recent review consisting of 20 randomized controlled trials with over 1500 patients with tennis elbow reported limited robust evidence recommending PRP therapy for lateral epicondylitis, attributed to heterogeneity in PRP formulation and lack of characterization causing differing outcomes [62]. To overcome the limitations presented by PRP, the potential to use other APBOs to manage lateral epicondylitis has been investigated.

A study with a medium risk of bias and a very low score on methodological quality showed that three injections of PL administered every fourth week in patients with elbow pain resulted in improvement in pain at 6-month follow-up compared to baseline and contralateral arm [60]. Tan et al. demonstrated that three weekly doses of PL administered in patients with lateral epicondylitis are safe and resulted in reduced pain and improved function at 12-month follow-up and decreased inflammation at 1-month follow-up compared to the baseline [45]. This study had a low risk of bias and a very low score on methodological quality. The exact mechanism of action for the efficacy of PL in tendon healing is not completely understood, though it can be attributed to the presence of numerous bioactive growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF) and fibroblast growth factors (FGF), which could influence tissue healing via angiogenesis, cellular chemotaxis, reconstruction of extracellular matrix, activating anabolic pathways and production of anti-inflammatory cytokines [63–65].

In a study with a low risk of bias and a very low score on methodological quality, four doses of ACS administered twice a week in patients with lateral epicondylitis resulted in reduced pain and improved function at 3-month and

Table 3 Generalities of the included studies

Author, year [Reference]	Journal	Follow-up (months)	Treatment group	Patients (*n*)	Women (*n*)	Mean age (years)
Scudeller et al., 2011 [60]	*BMJ*	6	PL	1	1	40
Tan et al., 2016 [45]	*J Orthop Surg Res*	12	PL	56	35	45
Ipek et al., 2022 [46]	*Arch Iran Med*	12	ACS	42	21	38

Table 4 Ongoing clinical trials registered on ClinicalTrials.gov, Clinical Trials Registry—India, and Chinese Clinical Trial Register until December 27, 2024, evaluating the safety and/or efficacy of autologous peripheral blood-derived orthobiologics for the management of elbow disorders

Study identifier	Autologous peripheral blood-derived orthobiologic	Study phase; Estimated enrollment (*N*)	Primary outcome measure(s)	Recruitment status	Study location(s)
NCT01668862	Autologous platelet lysate	Phase I/II; *N* = 20	Change in Visual Analog Score [time frame: day 0, month 1, month 2, end of study—month 3]	Unknown	India

1 year follow-up compared to the baseline [46]. Similar to PL, the mechanism of action for the efficacy of ACS in tendon healing is still unknown; it can be attributed to increased levels of anti-inflammatory cytokines, including interleukin-1-receptor antagonist (IL-1RA), IL-10, IL-14, and transforming growth factor – beta (TGF-β) [66–68].

Only one clinical trial was listed on various clinical trial protocol repositories (NCT01668862). This study aims to evaluate the safety and efficacy of PL in patients with lateral epicondylitis. The primary outcome measure included the assessment of VAS score at 3-month follow-up compared to baseline. The other outcome measures include, patient rated tennis elbow evaluation (PRTEE score), The American Shoulder and Elbow Society (ASES) score, and changes in ultrasonography of the lateral epicondyle region.

The present review has limitations, including the inclusion of only three clinical studies across various APBOs that met our inclusion criteria. This narrows the capacity to critically assess the efficiency of individual APBOs in managing elbow disorders. The included studies also have shortfalls, including short follow-up, small sample size, and absence of a placebo or active comparator. In addition, there is a risk of publication bias, as articles with favorable results are more prone to be accepted and published, which can lead to inadequate interpretation of the overall efficacy of APBOs. Therefore, more prospective, sufficiently powered, multi-center, controlled, randomized, and non-randomized studies with long follow-ups are needed to determine the ability of various APBOs to manage elbow disorders. Additional comparative studies are also required to aid clinicians in determining the ideal APBO to manage elbow disorders. Ideally, the various ABOs should be tested in a head-to-head fashion to ascertain their efficacy and effectiveness in elbow ailments.

CONCLUSIONS

The current peer-reviewed published studies demonstrated that administering APBOs,

including PL and ACS, might be safe and effective in reducing pain and improving function in patients with elbow disorders. Further high-quality studies are strongly required.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Ashim Gupta conceptualized the study. Ashim Gupta, Filippo Migliorini, and Tommaso Bardazzi wrote the initial draft. Ashim Gupta, Filippo Migliorini, Tommaso Bardazzi and Nicola Maffulli commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Ashim Gupta is an Editorial Board member of Pain and Therapy. Ashim Gupta was not involved in the selection of peer reviewers for the manuscript or any of the subsequent editorial decisions. Ashim Gupta declare that he has no other competing interests. Filippo Migliorini, Tommaso Bardazzi, and Nicola Maffulli declares that they have no competing interests.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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