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REVIEW

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

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ABSTRACT

Introduction: A multidisciplinary approach is recommended to manage shoulder pain, the third most common musculoskeletal disorder, but traditional modalities have limitations, providing only temporary symptomatic pain relief instead of targeting the underlying pathophysiology. Recently, autologous peripheral blood-derived orthobiologics (APBOs) have become popular for the management of shoulder disorders. Platelet-rich plasma (PRP) is the most frequently used APBO, but its efficacy remains disputable. Thus, the possibility of using other APBOs, such as platelet lysate (PL), autologous conditioned serum (ACS), gold-induced cytokine (GOLDIC), plasma rich in growth factors (PRGF), growth factor concentrate (GFC), autologous protein solution (APS), and hyperacute serum (HS), for the management of shoulder disorders have been considered. This review summarizes the outcomes of clinical studies involving APBOs to manage shoulder disorders.

Methods: Multiple databases (PubMed, Web of Science, Embase, and Scopus) were searched employing terms for APBOs and various shoulder disorders for articles published in the English language to September 11, 2024, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: Only six clinical studies fulfilled our pre-defined search and inclusion criteria. Specifically, one, two, two, and one studies involving the use of PL, ACS, PRGF, and APS, respectively, were included in this review. No clinical studies were identified involving the use of GOLDIC, GFC, and HS.

Conclusions: Administration of PL, ACS, PRGF, and APS is safe and can reduce pain and improve function in patients with shoulder disorders, including rotator cuff tendinopathy, subacromial impingement syndrome, glenohumeral osteoarthritis and delayed union fracture of the clavicle. Given the dearth of relevant literature and limitations of the available studies, more prospective clinical studies, and ideally, randomized controlled trials, with extended

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follow-up are necessary to establish the efficacy of APBOs and to select the ideal APBO for the management of shoulder disorders.

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

Key Summary Points
Administration of platelet lysate (PL), autologous conditioned serum (ACS) and plasma rich in growth factors (PRGF) in patients with rotator cuff tendinopathy is safe and can lead to reduced pain and improved function.
Administration of autologous protein solution (APS) in patients with subacromial impingement syndrome is safe and can reduce pain.
Administration of ACS in patients with glenohumeral osteoarthritis resulted in reduced pain, improved function, and delayed need for total shoulder replacement.
Administration of PRGF to patients with delayed union fracture of the clavicle can reduce pain and restore mobility of the shoulder.

INTRODUCTION

Musculoskeletal (MSK) disorders affect billions of individuals across the globe, significantly influencing their quality of life (QoL) [1]. Shoulder pain, behind low back and knee pain, is the third most common MSK disorder [1]. Its incidence grows with the level of activity and age of an individual, especially beyond the age of 50 years, with a lifetime occurrence of approximately 70% [1–4]. Shoulder pain can arise as a result of several conditions, including rotator cuff injuries, instability of the glenohumeral joint, osteoarthritis, frozen shoulder, and/or acromioclavicular joint disorders [1–3]. These conditions, in addition to pain, produce a reduced range of motion and function, and impede activities of daily living (ADL) [1–3]. Management of shoulder pain involves a multidisciplinary approach, including activity modification, physiotherapy, oral non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, local anesthesia, neurolysis, and/or surgery [1–3]. These typical treatment modalities have shortcomings, and usually give only temporary symptomatic pain relief rather than targeting the underlying pathophysiology [1–3, 5–8].

Recently, orthobiologics, including autologous peripheral blood-derived orthobiologics (APBOs), have become popular for the management of MSK conditions [9]. Platelet-rich plasma (PRP) is the most commonly used APBO, and several systematic reviews and meta-analyses have demonstrated its safety and efficacy for the management of various shoulder disorders [10–12]. Nevertheless, the efficacy of PRP remains disputable, given the non-uniform preparation protocol and characterization and patient variables [1, 9]. To overcome the limitations posed by PRP, the possibility of using other APBOs, such as platelet lysate (PL), autologous conditioned serum (ACS), gold-induced cytokine (GOLDIC), plasma rich in growth factors (PRGF), growth factor concentrate (GFC), autologous protein solution (APS), and hyperacute serum (HS), for the management of shoulder disorders have been considered. However, there are limited reviews summarizing the outcomes of clinical studies evaluating the effectiveness of these APBOs for the management of shoulder disorders. Thus, the primary objective of this review is to sum up the results of clinical studies involving the aforementioned APBOs to manage shoulder disorders. The secondary objective is to record the ongoing clinical studies listed on various clinical trial protocol repositories involving these APBOs for the treatment of shoulder disorders.

METHODS

Ethics Approval and Search Criteria

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

A search was performed using terms ('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 ('growth factor concentrate' OR 'GFC') or ('autologous protein solution' or 'APS') or ('hyperacute serum' OR 'HS' OR 'hypACT') AND ('shoulder') or ('rotator cuff') or ('glenohumeral joint') or ('shoulder osteoarthritis') or ('adhesive capsulitis' OR 'frozen shoulder') or ('acromioclavicular joint'), in several electronic databases, including PubMed, Web of Science, Embase, and Scopus, for articles published to September 11, 2024, in the English language, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All clinical studies using the aforesaid APBOs to manage different shoulder disorders were included (Fig. 1). Studies not involving the aforementioned APBOs alone or not targeting shoulder pathologies were excluded. The comparators can be baseline, placebo and/or active modalities (e.g., physiotherapy, NSAIDs, Corticosteroids, etc.). The outcome measures included patient-reported outcome measures (PROMs), such as visual analog scale (VAS), and other clinical measures, such as range of motion (ROM).

To minimize the risk of bias, both authors discussed and reviewed all the selected articles, references, and excluded articles from the study; any disagreements were resolved after a thorough discussion. All the data were extracted and analyzed by the first author, and then reviewed and approved by the second author.

In addition, ongoing clinical studies concerning the use of the above-mentioned APBOs to manage various shoulder disorders, registered on different protocol repositories, including ClinicalTrials.gov, Clinical Trials Registry—India (CTRI), and Chinese Clinical Trial Register (ChiCTR) using the search terms above, were documented.

RESULTS

Platelet Lysate (PL)

PL is derived from PRP and formulated via a double freeze/thaw cycle (freeze at – 80 °C and thaw at 37 °C) (Table 1) [9, 13]. Only one study involving PL to manage shoulder disorders met our inclusion criteria (Table 2).

A randomized, controlled, double-blind study investigated the efficacy of PL compared to

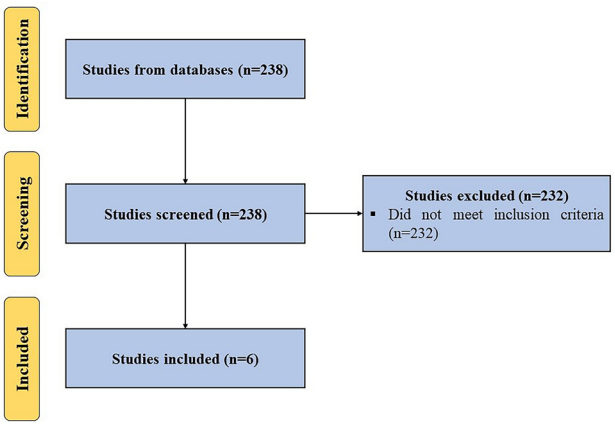

Fig. 1 A PRISMA flow diagram outlining the record identification and selection process

Table 1 A brief description of various autologous peripheral blood-derived orthobiologics (APBOs) included in this study

APBOs	References	Description
Platelet lysate (PL)	[9, 13]	PL is derived from platelet-rich plasma (PRP) and formulated via a double freeze/thaw cycle (freeze at − 80 °C and thaw at 37 °C)
Autologous conditioned serum (ACS)	[9, 15]	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, followed by centrifugation of the blood to collect serum
Gold-induced cytokine (GOLDIC)	[9]	GOLDIC is a type of ACS formulation which involves incubation of the whole blood with gold particles
Plasma rich in growth factors (PRGF)	[9]	PRGF is formulated by activating erythrocyte- and leukocyte-poor PRP with calcium chloride
Growth factor concentrate (GFC)	[9, 20]	GFC is an acellular formulation rich in platelet-derived growth factors, prepared by incubating whole blood with an external platelet activator
Autologous protein solution (APS)	[9, 21]	APS is formulated by incubating leukocyte-rich PRP with polyacrylamide beads
Hyperacute serum (HS)	[9, 23]	HS is formulated by mechanically releasing, via pressing or centrifugation, growth factors and cytokines from the platelet-rich fibrin clot

Table 2 Summary of main findings of clinical studies involving platelet lysate (PL) for the management of shoulder disorders

Author [Reference]	Type of study	Main findings
Markazi et al. [14]	Randomized, controlled, double-blind study	Three weekly subacromial injections of PL in patients with rotator cuff tendinopathy led to statistically significant improvements in VAS, SPADI and ROM at 6-month follow-up compared to the baseline and ketorolac tromethamine

PL platelet lysate, *VAS* Visual Analog Scale, *SPADI* Shoulder Pain And Disability Index, *ROM* range of motion

ketorolac tromethamine (KT) in patients with rotator cuff tendinopathy. The study included patients between 18 and 75 years of age, diagnosis of rotator cuff tendinopathy clinically or via imaging with symptoms for ≥ 3 months, pain in shoulder and/or lateral deltoid part, reduced ROM, no glucocorticoid injection in last 12 weeks, and failed conservative treatments. The study excluded patients < 18 years or > 75 years old, with full-thickness tears diagnosed via magnetic resonance imaging (MRI), prior history of surgery in the affected shoulder, infectious or auto-immune diseases, NSAIDs use in the previous week, and history of subacromial or intra-articular corticosteroid injection within the last 6 weeks. A pure PRP formulation with platelet concentration 4.2–4.6 times above baseline whole blood levels was formulated, followed by double freeze/thaw cycles to prepare the PL. Forty patients were randomized ($n = 20$ per group) to receive subacromial injections of either PL (1 ml, three weekly doses) or

KT (30 mg, two biweekly doses). The outcome measures included VAS, Shoulder Pain And Disability Index (SPADI) and ROM, which were assessed at baseline and after 1 and 6 months. No infections were reported in either group. Both groups showed statistically significant improvements in VAS, SPADI, and ROM abduction at each follow-up time-point compared to baseline. Only the PL group showed statistically significant improvements in internal rotation at 1- and 6-month follow-up compared to the baseline. In addition, the PL group showed statistically significant improvements in all PROMs at 6-month follow-up compared to the KT group. The limitations of this study include small cohort size and short follow-up. Administration of PL in patients with rotator cuff tendinopathy led to greater improvements in pain and function compared to KT injection over a 6-month follow-up [14].

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, followed by centrifugation of the blood to collect serum (Table 1) [9, 15]. Two studies involving ACS to manage shoulder disorders met our inclusion criteria (Table 3).

A prospective, randomized, double-blind, controlled study investigated the safety and efficacy of ACS injection compared to glucocorticoid (betamethasone) injection in patients with chronic supraspinatus tendinopathy. The inclusion criteria included patients with

Table 3 Summary of main findings of clinical studies involving autologous conditioned serum for the management of shoulder disorders

Author [References]	Type of study	Main findings
Damjanov et al. [16]	Prospective, randomized, double-blind, controlled study	Administration of four doses of ACS injected every week in patients with chronic shoulder pain due to supraspinatus tendinopathy is safe and led to statistically significant improvements in VAS and CSS scores at 24-week follow-up compared to the baseline and glucocorticoid
Simon et al. [17]	Longitudinal observational study	Intra-articular injection of six weekly doses of ACS in patients with glenohumeral (GH) osteoarthritis (OA) led to statistically significant improvements in VAS, SPADI, ASES, CS and ROM at 3–6-month follow-up compared to the baseline. In addition, it delayed the necessity of TSR in 53% of the patients with GH OA and led to significant improvements in VAS and SPADI at > 2 years (average 3.6 years) follow-up

ACS autologous conditioned serum, *VAS* Visual Analog Scale, *CSS* Constant Shoulder Score, *SPADI* Shoulder Pain And Disability Index, *ASES* American Shoulder and Elbow Surgeons, *CS* constant score, *ROM* range of motion

supraspinatus tendinopathy, at least 18 years of age, VAS ≥ 50 mm, have pain for ≥ 6 weeks, no other treatment in last 2 months and no history of trauma. Patients with acute shoulder pain were allowed to take 500 mg of paracetamol every 4 h, as needed. The exclusion criteria included glucocorticoid injection in the shoulder within the past 24 weeks, patients with contraindication to glucocorticoids, other inflammatory or auto-immune diseases, and patients with partial or complete supraspinatus tear or impingement (on ultrasonography). Patients were randomized 1:1; the ACS group received four weekly injections (2 ml per injection), whereas the glucocorticoid group received three weekly injections of betamethasone and a saline (placebo) injection in the fourth week. The ACS was formulated using Orthokine® (Orthogen Lab Services GmbH, Germany), following the manufacturer's instructions. The injections were administered into the enthesis and paratenon of the supraspinatus tendon. Safety was assessed over 24 weeks via analysis of adverse events (AE). For efficacy, the PROMs included VAS score for pain and Constant Shoulder Score (CSS) for function, assessed at weeks 0 (baseline), 4, and 24. Thirty-two patients (21 females and 11 males), 16 patients/group, were enrolled in this study. Eight transient AE were reported in the glucocorticoid group, but no AE were observed in the ACS group. No severe AE were reported in either group. The ACS group showed significant improvements in the VAS score at 4 and 24 weeks compared to baseline; the glucocorticoid group showed significant improvement at 4 weeks only. No significant differences were observed between the two groups at 4 weeks, but the improvement in the ACS group was significantly higher compared to the glucocorticoid group at 24 weeks. In addition, both groups showed significant improvements in the CSS score at 4 and 24 weeks compared to baseline. No significant differences were observed between the groups at 4 weeks, but the improvement in the ACS group was significantly higher compared to the glucocorticoid group at 24 weeks. The limitations of this study include small cohort size, short follow-up, absence of a placebo control group, and lack of imaging analysis. Administration of ACS in patients with chronic shoulder pain from supraspinatus tendinopathy is safe and led to better improvements in pain and function compared to glucocorticoid injection over a 24-week follow-up [16].

A longitudinal observational study investigated the efficacy of intra-articular injection of ACS in patients with glenohumeral (GH) osteoarthritis (OA). The inclusion criteria included patients older than 30 years, radiographic confirmation of GH OA (grade II–III, on Kellgren–Lawrence scale), and presence of pain, stiffness and disability. The exclusion criteria included patients with direct indication for total shoulder replacement (TSR) (grade IV OA), crystalline or inflammatory arthropathy, and inability to get six weekly injections. Thirty-six patients (40 shoulders) were enrolled in this study and received six weekly intra-articular injections of ACS (2 ml per injection). The outcome measures included PROMs, such as VAS, SPADI, American Shoulder and Elbow Surgeons (ASES) score and Constant score (CS), and other clinical measures, such as ROM, assessed at baseline and at 3–6 months of follow-up. A second follow-up was performed at a minimum of 2 years to determine whether the patients progressed to TSR, and, in patients who did not, VAS and SPADI scores were recorded. Of 40 shoulders, two were lost to follow-up, and four patients decided to undergo TSR. The results demonstrated statistically significant improvements in the VAS, SPADI, ASES, CS, and ROM (passive external rotation, passive GH abduction, and active elevation) at 3–6 months of follow-up compared to the baseline. In addition, 18 of 34 (53%) shoulders did not undergo TSR (average 3.6 years follow-up) and showed statistically significant improvements in both the VAS and SPADI scores. The limitations of this study include its small cohort size and absence of placebo/control group. Intra-articular administration of ACS in patients with GH OA led to reduced pain, improved function, and delayed necessity for TSR [17].

Gold-Induced Cytokine (GOLDIC)

GOLDIC is a type of ACS formulation that involves incubation of the whole blood with

gold particles (Table 1) [9]. To date, there are no published clinical studies involving the use of GOLDIC for the management of shoulder disorders.

Plasma Rich in Growth Factors (PRGF)

PRGF is formulated by activating erythrocyte- and leukocyte-poor PRP with calcium chloride (Table 1) [9]. Two studies involving PRGF to manage shoulder disorders met our inclusion criteria (Table 4).

Seijas et al. evaluated the efficacy of PRGF in a case report of delayed union of a fracture of the clavicle. Briefly, a 44-year-old female fell sustaining a distal left clavicle fracture, and did not want surgery. The patient reported pain and functional limitations, including restricted flexion of the arm during abduction, 8 months after the injury. Plain radiographs showed atrophic delayed union clavicle fracture. PRGF was prepared as per manufacturer's (Biotechnology Institute, Spain) instructions. Three percutaneous injections of PRGF, administered biweekly, were performed into the delayed union fracture site. Three months after administration of the last dose, a computed tomography (CT) was performed and healing of the clavicle was observed. The patient reported no pain, full shoulder mobility and ability to perform all normal life activities [18].

A prospective, double-blind RCT investigated the efficacy of intratendinous injection of PRGF compared to corticosteroid in patients with chronic rotator cuff tendinopathy. The inclusion criteria included patients between the age of 40 and 70 years, moderate to severe symptoms (on Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) score) within the last 3 months, calcific or inflammatory tendinopathy, or partial rotator cuff tear, diagnosed via MRI or ultrasound, and patients non-responsive to conservative treatments. The exclusion criteria included patients with complete rotator cuff tear, treatment with infiltrations in the last 6 months, and contraindication to corticosteroids. PRGF was prepared as per manufacturer's (Biotechnology Institute, Spain) instructions. Eighty-four patients were randomized 1:1 to receive an injection intratendinously and in the subacromial space of either PRGF (6–8 ml, three biweekly doses) or corticosteroid (2 ml Celestone Cronodose and 4 ml mepivacaine, three biweekly doses). The PROMs included University of California Los Angeles (UCLA) scale, QuickDASH and Constant–Murley (CM) score, assessed at baseline and at 3-, 6-, and 12-month

Table 4 Summary of main findings of clinical studies involving plasma rich in growth factors for the management of shoulder disorders

Author [References]	Type of study	Main findings
Seijas et al. [18]	Case report	Administration of three biweekly percutaneous injections of plasma rich in growth factors (PRGF) into the delayed union fracture of the clavicle can reduce pain and restore mobility of the shoulder
Vaquerizo et al. [19]	Double-blind, randomized controlled trial	Administration of three biweekly intratendinous injections of PRGF in patients with chronic rotator cuff tendinopathy led to significant improvements in pain and function compared to the baseline and corticosteroid group over a 12-month follow-up

follow-up. All PROMs showed statistically significant improvements for both groups at all follow-up time points compared to baseline. In addition, the PRGF group showed statistically significant improvements in all PROMs at all time points compared to the corticosteroid group, except for the UCLA scale at 3-month follow-up. The limitations of this study include small cohort size, short follow-up, and lack of imaging analysis. Administration of PRGF in patients with chronic rotator cuff tendinopathy led to significant improvements in pain and function compared to the baseline and corticosteroid group over a 12-month follow-up [19].

Growth Factor Concentrate (GFC)

GFC is an acellular formulation rich in platelet-derived growth factors, prepared by incubating whole blood with an external platelet activator (Table 1) [9, 20]. To date, there are no published clinical studies involving the use of GFC for the management of different shoulder disorders.

Autologous Protein Solution (APS)

APS is formulated by incubating leukocyte-rich PRP with polyacrylamide beads (Table 1) [9, 21]. Only one study involving APS to manage shoulder disorders met our inclusion criteria (Table 5).

A randomized study investigated the feasibility of recruiting and retaining patients along with evaluating the safety and efficacy of APS compared to the corticosteroid in patients with subacromial pain. The inclusion criteria included patients older than 18 years and a clinical diagnosis of subacromial impingement syndrome. The exclusion criteria included patients with a history of shoulder trauma in last 5 years, contraindication to APS or corticosteroid, history of neurogenerative and/or vascular conditions affecting the function of the shoulder, and prior injection of APS or corticosteroid in the last 2 months. Fifty patients were randomized 1:1 to receive either a subacromial injection of APS (~ 3 ml) or corticosteroid (40 mg Depo-Medrone in 3 ml 0.5% bupivacaine). APS was formulated using nSTRIDE® (Zimmer Biomet, USA). The primary outcome measures included rates of recruitment, retention, and compliance to determine feasibility. The secondary outcome measures included Patient-Reported Outcomes Measurement Information System (PROMIS) upper limb physical function, PROMIS pain interference, Oxford Shoulder Score (OSS), VAS, EuroQoL five-dimension five-level (EQ-5D-5L), Work Productivity Impairment Questionnaire (WPAI), health resource use and complications questionnaire, assessed at baseline and at 3- and 6-month follow-up. No severe AE were reported throughout the duration of this study. Forty-nine patients (98%) complied with the study, and outcomes data were collected for 100% and 94% of the participants at 3- and 6-month follow-up, respectively. All PROMs showed improvement for both groups at 6-month follow-up. The limitations of this study include lack of comparative statistical analysis given the small cohort size and absence of placebo control. The results demonstrated feasibility to recruit and retain patients in a blinded RCT comparing APS and corticosteroid. In addition, the administration of APS and corticosteroid is safe and potentially efficacious for the management of subacromial pain [22].

Table 5 Summary of main findings of clinical studies involving autologous protein solution for the management of shoulder disorders

Author [Reference]	Type of study	Main findings
Woods et al. [22]	Randomized feasibility study	It is feasible to recruit and retain patients in a blinded randomized controlled trial comparing autologous protein solution (APS) and corticosteroid; and subacromial injection of both APS and corticosteroid is safe and potentially efficacious for the management of subacromial pain due to subacromial impingement syndrome

Hyperacute Serum (HS)

HS is formulated by mechanically releasing, via pressing or centrifugation, growth factors and cytokines from the platelet-rich fibrin clot (Table 1) [9, 23]. To date, there are no published clinical studies involving the use of HS for the management of different shoulder disorders.

Ongoing Clinical Trials

As of September 11, 2024, no clinical trials were listed on ClinicalTrials.gov, CTRI, or ChiCTR to evaluate the safety and/or effectiveness of aforementioned APBOs to manage shoulder disorders.

DISCUSSION

The present study evaluated the therapeutic potential of various APBOs, including PL, ACS, GOLDIC, PRGF, GFC, APS and HS, for the management of shoulder disorders. All clinical studies using APBOs to manage various shoulder disorders were included. Based on our pre-defined search and inclusion criteria, six studies met the scope of our manuscript. Specifically, one, two, two, and one studies involving the use of PL, ACS, PRGF and APS, respectively, were included in this review. No clinical studies were identified involving the use of GOLDIC, GFC and HS for the management of shoulder disorders. No ongoing clinical studies were registered on either of the searched trial protocol repositories involving the use of aforementioned APBOs.

Rotator cuff tendinopathy is one of the most common causes of shoulder pain, dysfunction, and discomfort in adults, significantly affecting their QoL [24]. Several studies assessed the effectiveness of PRP for rotator cuff tendinopathy, but there is no consensus regarding its routine use, attributed to varying characteristics and inconsistent outcomes [25, 26]. To circumvent the limitations posed by PRP, the prospect of using other APBOs for the management of rotator cuff tendinopathy has been explored. Markazi et al. demonstrated that three weekly subacromial injections of PL in the patients with rotator cuff tendinopathy resulted in statistically significant improvement in various PROMs, such as VAS and SPADI, and ROM at 6-month follow-up compared to the baseline and ketorolac tromethamine [14]. Damjanov et al. demonstrated that four doses of ACS injected every week in patients with supraspinatus tendinopathy are safe, and resulted in statistically significant improvements in PROMs, such as VAS and CSS scores, at 24-week follow-up compared to the baseline and glucocorticoid [16]. Vaquerizo et al. demonstrated that three biweekly intratendinous injections of PRGF in patients with chronic rotator cuff tendinopathy resulted in significant improvements in pain and function compared to the baseline and corticosteroid group over a 12 month follow-up [19].

Subacromial impingement syndrome is the most common cause of shoulder pain, accounting for 44–65% of all shoulder complaints [27]. Several studies investigated the effectiveness of PRP to manage subacromial pain from subacromial impingement syndrome but were unable to establish the superiority of PRP over exercise therapy and/or corticosteroid injection [28, 29]. Woods et al. investigated the efficacy of APS, as an alternate to PRP, in patients with subacromial pain [22]. Even though, conceptually, PRP and APS are similar, as both involve isolation of anti-inflammatory cytokines and anabolic growth factors from patient's peripheral blood, APS favorably concentrates anti-inflammatory cytokines, such as interleukin-1 receptor antagonist and tumor necrosis factor receptor inhibitor, from leukocytes [30]. A subacromial injection of APS is safe and potentially efficacious for the management of subacromial pain arising from subacromial impingement syndrome [22].

The GH joint, after the knee and the hip, is the third large joint most commonly affected by OA, with chronic and persistent shoulder pain [31]. There is scarcity of studies evaluating the effectiveness of various orthobiologics, including APBOs, such as PRP, to manage GH OA [31]. A recent RCT showed that administration of leukocyte poor PRP led to significant improvement in PROMs, such as SPADI score, compared to the baseline at 12-month follow-up; however, no significant improvements were observed compared to the control, namely

hyaluronic acid, group [32]. This suggests the need for more studies to further evaluate the efficacy of PRP to manage GH OA. In addition, the possibility of using other APBOs for GH OA was contemplated. Simon et al. demonstrated that six weekly intra-articular doses of ACS in patients with GH OA resulted in statistically significant improvements in various PROMs, such as VAS, SPADI, ASES, and CS scores, and ROM at 3–6 months of follow-up compared to baseline [17]. The administration of ACS also resulted in delayed necessity for TSR in 53% of the patients and statistically significant improvements in PROMs, such as VAS and SPADI, after an average 3.6-year follow-up [17].

Clavicle fractures are common, but non-unions are rare [33, 34]. Several studies have shown the potential of various orthobiologics, including PRP, for the management of delayed union and non-union fractures [35]. However, no study to date has investigated the efficacy of PRP alone for the management of delayed union or non-union fracture of the clavicle. The ability of PRP to aid fracture repair can be attributed to growth factors derived from platelets, which can trigger proliferation and chemotaxis of chondrocytes, osteoblasts, and mesenchymal stem cells [18]. Yet, variability in the formulation protocols and resultant differing growth factor concentrations, leading to varied therapeutic outcomes, have warranted consideration of other APBOs to manage delayed union or non-union of fractures of the clavicle. Three biweekly percutaneous injections of PRGF into the delayed union fracture of the clavicle can reduce pain and restore mobility of the shoulder [18].

The presented investigation has limitations, including the inclusion of only six clinical studies across various APBOs which fulfilled our predefined search and inclusion and exclusion criteria. This confines the ability to critically examine the efficacy of individual APBOs for the management of shoulder disorders. The included studies also have inadequacies, including small cohort size and short follow-up. This can lead to inflated effect sizes resulting in misleading interpretations, higher chance of type II errors, non-detection of long-term adverse events and non-assessment of results from increased likelihood of dropout in studies with longer follow-up. In addition, there is a risk of publication bias, as reports with positive results are more likely to be published, probably resulting in inadequate representation of the overall effectiveness of different APBOs for the management of shoulder disorders. Thus, more prospective, sufficiently powered, multi-center, non-randomized and randomized controlled trials with adequate follow-up are necessary to prove the efficacy of various APBOs in managing shoulder disorders. Further comparative studies to aid physicians/surgeons in selecting the best APBO for the management of shoulder disorders are also needed.

CONCLUSIONS

The existing published peer-reviewed literature suggests that the administration of APBOs, including PL, ACS, PRGF and APS is safe and can reduce pain and improve function in patients with shoulder disorders, including rotator cuff tendinopathy, subacromial impingement syndrome, GH OA, and delayed union fracture of the clavicle.

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 and wrote the initial draft. Ashim Gupta 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 nor any of the subsequent editorial decisions. Ashim Gupta declares that he has no other competing interests. Nicola Maffulli declares that he has 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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