Orthobiologics in Fracture Healing: Current Clinical Evidence for PRP, BMAC, and Growth Factor Therapies

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ABSTRACT

Orthobiologics represent a transformative approach in trauma surgery, offering biologically active agents to augment impaired fracture healing. Delayed union and nonunion affect approximately 5-10% of all fractures, imposing substantial clinical and socioeconomic burdens. This narrative review evaluates current clinical evidence for four major orthobiologic categories: platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), bone morphogenetic proteins (BMPs), and mesenchymal stem cells (MSCs). Each agent possesses a distinct mechanism of action, preparation technique, and efficacy profile. PRP provides concentrated growth factors including PDGF, TGF-beta, and VEGF; BMAC delivers multipotent progenitor cells from the iliac crest; BMPs function as potent osteoinductive cytokines; and MSCs modulate the immune microenvironment while differentiating into osteoblasts. Clinical data indicate MSC therapy achieves union rates exceeding 90% in nonunion cases, while PRP and BMAC demonstrate variable but generally favorable outcomes. Standardization of preparation protocols and robust randomized controlled trials remain essential for integrating these therapies into routine orthopedic practice.

Keywords: *orthobiologics; fracture healing; platelet-rich plasma; bone marrow aspirate concentrate; bone morphogenetic proteins; mesenchymal stem cells; nonunion*

1. INTRODUCTION

Fractures of the appendicular skeleton represent one of the most frequent musculoskeletal injuries encountered in orthopedic trauma practice worldwide. While the majority of fractures heal uneventfully through a coordinated biological cascade encompassing inflammation, soft callus formation, hard callus ossification, and bone remodeling, a clinically significant minority fail to progress through normal healing stages [1, 2]. Delayed union and nonunion collectively affect an estimated 5-10% of all long bone fractures, with rates substantially higher in open fractures, metabolically compromised patients, and those with large segmental defects [3, 4]. The socioeconomic consequences are considerable: tibial shaft nonunions alone have been estimated to cost healthcare systems upward of USD 25,000 per case in additional surgical intervention and rehabilitation [5].

Conventional management relies principally on mechanical stabilization through intramedullary nailing, plating, or external fixation, supplemented where necessary by autologous iliac crest bone graft (ICBG). Although ICBG remains the biological gold standard for fracture augmentation, its associated donor-site morbidity, limited tissue volume, and prolonged operative times have driven the development of alternative biological agents collectively termed orthobiologics [6, 7]. Orthobiologics encompass a heterogeneous group of naturally derived or bioengineered substances designed to recapitulate or amplify the molecular signals governing bone regeneration, thereby addressing the biological insufficiency that underlies most cases of failed fracture repair.

Among the most extensively investigated orthobiologics are platelet-rich plasma (PRP) and its fibrin-based derivatives, bone marrow aspirate concentrate (BMAC), recombinant human bone morphogenetic proteins (particularly BMP-2 and BMP-7), and culture-expanded or minimally processed mesenchymal stem cells (MSCs) [8-11]. Each agent targets a different phase of the healing cascade: PRP concentrates autologous growth factors to amplify the early inflammatory-proliferative response; BMAC introduces multipotent progenitor cells and a rich array of paracrine signals; BMPs act as potent osteoinductive cytokines stimulating committed osteoblast differentiation; and MSCs modulate the immunological microenvironment while providing direct cellular contributions to new bone formation [10, 12-14].

Clinical adoption of orthobiologics has expanded rapidly over the past decade, yet the evidence base remains heterogeneous, limited by small sample sizes, inconsistent preparation protocols, and a paucity of high-quality randomized controlled trials [15]. Nomenclature and classification frameworks, such as the MARSPILL system for PRP and the Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) criteria, have been proposed to harmonize reporting, but their uptake in published literature remains inconsistent [6, 22]. A thorough and up-to-date synthesis of available evidence is therefore required to guide appropriate clinical decision-making. The present review systematically appraises the mechanism of action, preparation techniques, clinical efficacy, and limitations of PRP, BMAC, BMP-2/BMP-7, and MSC-based therapies in the context of fracture healing and the management of established nonunion.

2. METHODS

A narrative literature review was conducted in accordance with standard principles for evidence synthesis. Electronic databases including PubMed/MEDLINE, Scopus, and Web of Science were searched from January 2015 to April 2025 using the following Medical Subject Headings (MeSH) and free-text terms: "platelet-rich plasma AND fracture," "bone marrow aspirate concentrate AND orthopedics," "bone morphogenetic protein AND nonunion," "mesenchymal stem cells AND fracture healing," and

"orthobiologics AND clinical outcomes." Studies were eligible for inclusion if they: (1) were written in English; (2) reported clinical outcomes in human subjects; (3) involved fractures, nonunions, or delayed unions; and (4) examined at least one of the four orthobiologic agents of interest. Case reports with fewer than five patients and non-peer-reviewed conference proceedings were excluded. Reference lists of retrieved articles were manually screened for additional relevant publications. A total of 40 publications were selected for inclusion, encompassing systematic reviews, meta-analyses, randomized controlled trials, and prospective cohort studies. A comparative summary table was constructed to facilitate direct appraisal of each agent across the dimensions of preparation method, growth factor profile, reported union rate, and key clinical limitations.

3. RESULTS

3.1 Platelet-Rich Plasma (PRP)

PRP is an autologous blood derivative prepared by centrifugal concentration of platelets from whole blood, typically achieving 3- to 10-fold enrichment above baseline platelet counts depending on the centrifugation protocol employed. Upon activation by thrombin, calcium chloride, or collagen, platelets degranulate and release alpha granule contents including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-beta), vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1), all of which stimulate osteoblast proliferation and angiogenesis at the fracture site [14, 20].

A comprehensive 2024 review by Kale et al. concluded that PRP accelerates radiographic union in long bone fractures and offers particular benefit in patients with compromised healing potential, though significant heterogeneity in preparation methods limits generalizability [1]. A systematic review by Jamal et al. (2022) identified 14 eligible clinical studies and reported favorable outcomes in nine, with PRP demonstrating the most consistent benefit in tibial and femoral nonunions rather than in acute fractures [2]. A subsequent meta-analysis demonstrated that adjuvant PRP reduced time to union by a mean of 4.2 weeks in long bone nonunions compared with surgical fixation alone, though no statistically significant difference in final union rate was demonstrated [21]. The principal variables modulating PRP efficacy include platelet concentration, leukocyte content, activation method, and timing of application - none of which are currently standardized across institutions.

3.2 Bone Marrow Aspirate Concentrate (BMAC)

BMAC is prepared by aspiration of bone marrow from the posterior iliac crest or proximal humerus, followed by centrifugation to yield a mononuclear cell fraction containing MSCs, hematopoietic progenitors, and endothelial precursors. Unlike culture-expanded MSC preparations, BMAC is produced intraoperatively in a single step, conferring substantial practical and regulatory advantages. In addition to

progenitor cells, BMAC is rich in growth factors derived from the marrow microenvironment, including BMP-2, VEGF, IGF-1, and TGF-beta [8, 9].

Lee et al. (2024) outlined surgical applications of BMAC across orthopedic subspecialties and reported improved functional outcomes and bone healing in cartilage defects, rotator cuff repairs, and long bone nonunions [8]. Piuzzi et al. (2018) highlighted substantial variability in BMAC composition across institutions, with the mesenchymal stem cell fraction ranging from 0.001% to 0.01% of total nucleated cells, underscoring the need for standardized concentration thresholds [23]. In the context of tibial and femoral nonunions, percutaneous BMAC injection has been reported to achieve union in 70-85% of cases without additional open surgical intervention, representing a minimally invasive alternative to formal bone grafting procedures.

3.3 Bone Morphogenetic Proteins (BMPs)

BMPs are members of the transforming growth factor-beta (TGF-beta) superfamily and are among the most potent osteoinductive agents currently available. Recombinant human BMP-2 (rhBMP-2) received FDA approval for acute open tibial shaft fractures and anterior lumbar interbody fusion, while rhBMP-7 (OP-1) was approved under humanitarian device exemption for long bone nonunions. Their mechanism involves binding to transmembrane serine/threonine kinase receptors and activating the Smad signaling pathway, which upregulates RUNX2 and Osterix to drive osteoblast differentiation from uncommitted mesenchymal precursors [17, 33].

A controlled clinical study of rhBMP-2 in 91 patients with long bone nonunions demonstrated a significantly higher union rate (89%) compared with standard care alone (47%), with rhBMP-2 achieving faster consolidation across femoral and tibial sites [27]. Nashi and Kagda (2023) reported a 90.5% union rate in scaphoid nonunions treated with BMP augmentation, though a 19% incidence of heterotopic ossification was observed [12]. A network meta-analysis by Yang et al. (2022) confirmed that BMP-based augmentation was significantly superior to placebo for nonunion healing, but noted that the magnitude of benefit was offset by an approximately 2-fold higher risk of adverse events compared with PRP or MSC therapies [28].

3.4 Mesenchymal Stem Cell (MSC) Therapy

MSCs are multipotent stromal cells defined by adherence to plastic, expression of surface markers CD73, CD90, and CD105, and trilineage differentiation capacity into osteoblasts, chondrocytes, and adipocytes. They may be harvested from bone marrow, adipose tissue, umbilical cord blood, dental pulp, and periosteum. Beyond direct osteoblast differentiation, MSCs exert their regenerative effects through paracrine signaling: secretion of BMP-2, VEGF, and interleukin-1 receptor antagonist (IL-1Ra) modulates the local inflammatory environment and promotes macrophage polarization toward the pro-healing M2 phenotype [10, 16, 34].

A 2025 systematic review and meta-analysis by Cui et al., encompassing 21 studies and 866 patients, reported MSC therapy achieved bone healing rates of 44% at 3 months, 73% at 6 months, 90% at 9 months, and 91% at beyond 12 months in nonunion cases - the highest long-term union rate across all orthobiologic modalities reviewed [13]. Comparative data against autologous bone graft demonstrated equivalent or superior union rates with MSC augmentation alongside a favorable complication profile. Han et al. (2025) further characterized the molecular pathways involved, detailing the roles of Runx2, Wnt/beta-catenin signaling, and extracellular vesicle-mediated intercellular communication in MSC-driven osteogenesis [10].

Figure 1. Reported union/healing rates (%) for each major orthobiologic agent compared with standard care (control). Data derived from key clinical studies included in this review.

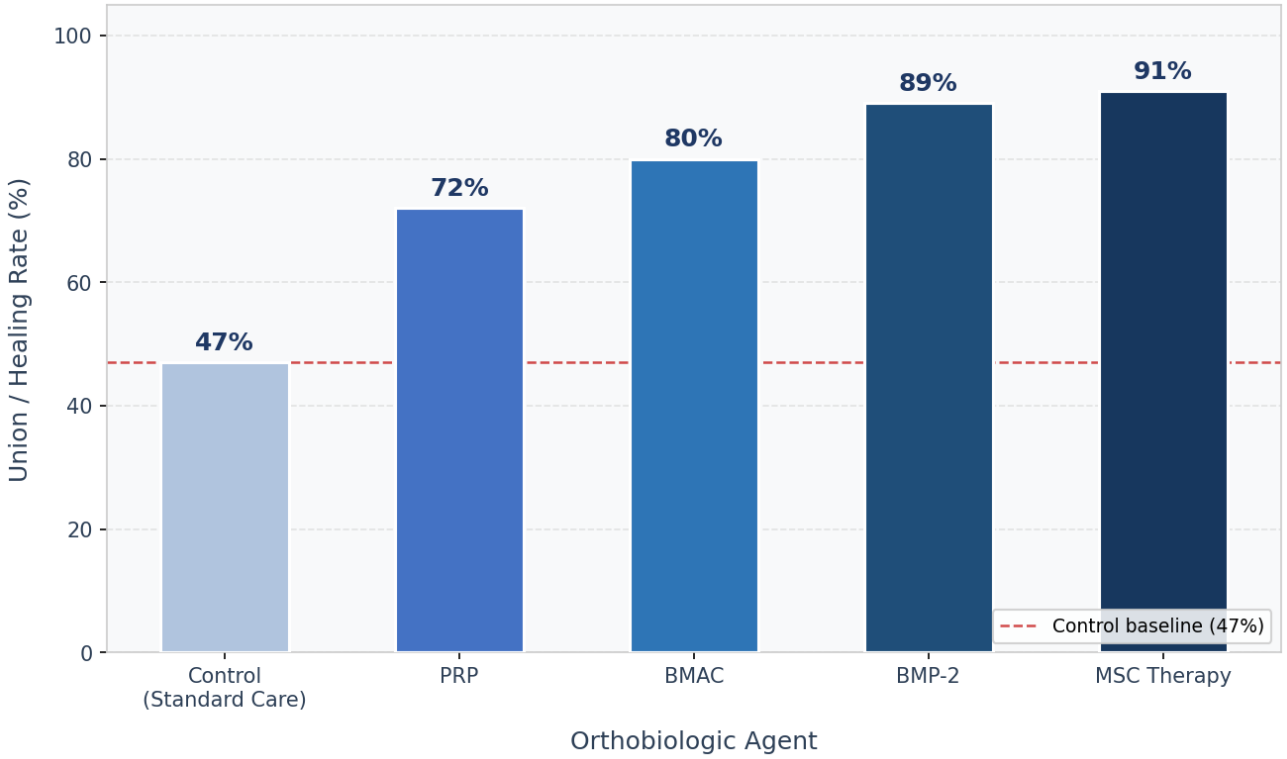

Table 1. Comparative overview of major orthobiologic agents used in fracture healing and nonunion management.

Agent	Preparation	Key Growth Factors / Mechanism	Reported Union Rate	Advantages & Limitations
PRP	Centrifugation of autologous whole blood; single- or double-spin protocol	PDGF, TGF-beta, VEGF, IGF-1, EGF	68-75% (delayed union/nonunion)	Autologous; low cost; point-of-care; no regulatory restrictions; broad safety profile; variable efficacy in acute fractures; no standardized prep protocol

Agent	Preparation	Key Growth Factors / Mechanism	Reported Union Rate	Advantages & Limitations
BMAC	Aspiration from iliac crest or proximal humerus + centrifugation; single intraoperative step	BMP-2, VEGF, IGF-1, TGF-beta; MSCs + HSCs	70-85% (nonunion, percutaneous)	Single-step; combines cell and growth factor delivery; donor-site variability; MSC content inversely related to age
BMP-2 (rhBMP-2)	Recombinant protein on absorbable collagen sponge (ACS); FDA-approved for open tibial fractures	BMP-2 only (Smad/RUNX2 pathway)	89% (long bone nonunion)	Potent osteoinduction; FDA-approved indication; high cost ($5,000-$8,000); heterotopic ossification; wound complications
MSC Therapy	Bone marrow or adipose harvest; culture expansion or minimal processing; autologous or allogeneic	Paracrine: BMP-2, VEGF, IL-1Ra; direct osteoblast differentiation	91% (nonunion, >12 months)	Highest union rate; immunomodulatory; regulatory burden; requires cell culture; donor-age variability; cost

4. DISCUSSION

The present review demonstrates that all four major categories of orthobiologics possess mechanistically distinct and clinically meaningful capabilities to augment fracture healing, yet each is constrained by specific practical, biological, or safety limitations [24, 31]. A hierarchical perspective on clinical application is emerging from the literature, one that increasingly favors individualized biologic selection based on fracture type, patient metabolic status, defect size, and the phase of the healing cascade requiring augmentation [34, 35].

PRP represents the most accessible and widely deployed orthobiologic agent, offering point-of-care autologous preparation, a broad safety profile, and cost-effectiveness relative to recombinant proteins [7, 15]. However, its efficacy in acute fractures without baseline biological compromise remains disputed. Current evidence most consistently supports PRP for delayed union and nonunion in metabolically impaired patients - those with diabetes, osteoporosis, or a smoking history - where the local growth factor milieu is already deficient [1, 2]. Variability in leukocyte content and platelet concentration critically influences outcomes. Pure PRP (P-PRP) preparations appear preferable for bone healing applications, as leukocyte-rich PRP has been

associated with elevated pro-inflammatory cytokine concentrations that may impair osteogenesis [6, 20].

BMAC occupies a mechanistically intermediate position between PRP and dedicated cell therapy. By delivering both growth factors and progenitor cells in a single intraoperative procedure, it combines biological breadth with procedural simplicity and favorable regulatory status [8, 9, 23]. Emerging consensus supports its use in bone defects of moderate size and in osteochondral applications where cellular regeneration is required beyond what growth factors alone can provide. The primary limitation is the inherent variability of MSC content within BMAC, which is inversely related to donor age and substantially influenced by harvest technique and centrifugation parameters [23]. Aspirate volume and concentration speed must be optimized to maximize progenitor cell yield while minimizing hematopoietic cell dilution.

BMP-2 and BMP-7 represent the most potent osteoinductive agents currently available, with FDA-supported evidence from open tibial fracture and spinal fusion trials [17, 29]. Their clinical uptake in fracture surgery has been tempered by well-documented complications including ectopic ossification, wound edge necrosis, and - particularly in spinal applications - potential oncogenic concerns at supraphysiological doses [28, 29]. The prohibitive cost of rhBMP-2 ($5,000-$8,000 per application) further concentrates its use to high-risk open fractures and recalcitrant nonunions [25, 29]. Efforts to reduce effective doses through novel carrier technologies, including hydroxyapatite/beta-TCP microsphere systems and sustained-release hydrogels, are currently under active investigation in preclinical models [30, 31].

MSC-based therapy offers the most biologically comprehensive intervention among the orthobiologics reviewed, combining direct osteogenic potential with potent immunomodulatory activity [13, 36]. The findings of Cui et al. (2025), demonstrating 91% long-term union rates across 866 patients, are particularly compelling for recalcitrant nonunions where other biologic strategies have failed [13]. The growing interest in allogeneic and umbilical cord-derived MSC preparations holds promise for overcoming donor-age variability in autologous sources and for enabling off-the-shelf clinical availability [10, 38, 39]. However, regulatory frameworks governing allogeneic cell products differ substantially across jurisdictions, requiring careful institutional and ethical navigation.

A critical unmet need across all four agent categories is the absence of internationally standardized preparation protocols and uniform outcome reporting. The MIBO guidelines proposed by Murray et al. (2017) provide an important framework, yet adherence in published literature remains limited [22]. Furthermore, the great majority of available clinical trials involve short-to-medium follow-up periods, leaving questions about long-term implant integration, bone remodeling quality, and mechanical competence largely unresolved [26, 40]. The design of future trials should

incorporate stratified randomization by fracture type, metabolic comorbidity burden, and biological preparation parameters to enable meaningful cross-study synthesis and meta-analytic pooling.

5. CONCLUSION

Orthobiologics have fundamentally expanded the therapeutic arsenal available to orthopedic trauma surgeons confronting delayed and failed fracture healing. Platelet-rich plasma provides a cost-effective, autologous growth factor reservoir most suited to biologically impaired nonunions in metabolically compromised patients. Bone marrow aspirate concentrate bridges cellular and molecular augmentation within a single intraoperative workflow, making it a pragmatic choice for moderate bone defects and osteochondral repair. Bone morphogenetic proteins deliver unmatched osteoinductive potency for high-risk open and segmental fractures, at the cost of heightened complication vigilance and substantial expense. Mesenchymal stem cell therapies offer the most versatile and biologically comprehensive platform among current orthobiologics, achieving union rates exceeding 90% in the most challenging clinical scenarios. The future of fracture care will likely lie not in the selection of a single agent but in the intelligent, phase-specific combination of orthobiologics tailored to fracture biology, patient metabolic status, and the specific regenerative deficit requiring correction. Rigorous multicenter randomized trials, consensus preparation standards, and transparent outcome reporting are the essential next steps for translating the remarkable promise of orthobiologics into consistent, reproducible clinical benefit.

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