Orthobiologics in Hand Surgery

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Planners

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Learning Objectives

Upon completion of this CME activity, the learner will understand:

- The current evidence regarding the use of orthobiologic agents for hand and wrist pathology.
- Which conditions in the hand and wrist may respond to treatment with orthobiologic agents.
- Outcomes associated with the use of orthobiologic agents in the hand and wrist.

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Orthobiologic agents are used as innovative adjuvant therapy to treat common upper-extremity pathology, including carpal tunnel syndrome, de Quervain tenosynovitis, and distal radius fractures. In this article, we perform a narrative review and evaluate current literature on orthobiologics in the upper extremity. Orthobiologics evaluated include bone morphogenetic proteins, platelet-rich plasma, bone marrow aspirate concentrate, mesenchymal stem cells, and amniotic membrane. Studies selected include randomized control trials, case studies, and animal studies. Although there is some clinical evidence regarding the

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use of orthobiologic agents in the treatment of shoulder, elbow, and sports injuries, there is a paucity of literature regarding their use to treat pathology of the hand and wrist. Further investigation is necessary to determine their effectiveness and therapeutic value in treatment of upper extremity injuries. *(J Hand Surg Am. 2021;46(5):409–415. Copyright © 2021 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Arthritis, carpal tunnel syndrome, orthobiologic agent, platelet-rich plasma, tendon rupture.

Biologic agents are increasingly being used in the treatment of orthopedic injuries. Orthobiologics are defined as derivatives of substances that naturally occur in the body and are thought to accelerate the healing of musculoskeletal pathology. Examples of such orthobiologics include growth factors or bone morphogenetic proteins (BMPs), platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), mesenchymal stem cells (MSCs), and amniotic membrane. Table 1 lists descriptions of these orthobiologic agents. Although there is some clinical evidence regarding the use of these agents in the treatment of musculoskeletal conditions of the shoulder and elbow and in sports injuries, there is a paucity of literature regarding the use of orthobiologics for the pathology of the hand, and the existing literature is of a variable but overall low level of evidence. The purpose of this article is to review the current literature and clinical evidence regarding the role of orthobiologic therapies for the treatment of hand and wrist conditions. Of note, reports on harvest technique as well as donor site morbidity are limited and are not covered here. Regulatory approvals of these agents are at various stages (Table 2), which may be important to consider prior to utilization.

DE QUERVAIN TENOSYNOVITIS

Few studies have reported the results of the effect of PRP in the management of de Quervain tenosynovitis. Ramesh et al[1] performed a longitudinal prospective cohort study on 840 patients with musculoskeletal conditions, including 141 patients with de Quervain tenosynovitis, to analyze the effects of autologous PRP injection. Nonoperative measures were not defined by the authors, the duration of non-surgical treatment was not clearly mentioned, and a comparison group (use of an orthosis or corticosteroid injection) was not included. Patients were evaluated 1, 3, and 6 months after injection. The authors found that 77% of patients had pain relief with the first autologous PRP injection, and an additional 16% of patients had pain relief after a second injection administered 3 weeks later. They also noted statistically significant improvements in pain relief and function. Peck and Ely[2] performed a case study in which the patient underwent ultrasound-guided percutaneous needle tenotomy of the first dorsal compartment followed by PRP injection for de Quervain tenosynovitis. The patient had previously failed other nonoperative measures of orthosis use, corticosteroid injection, and activity modification. At 6 months after undergoing percutaneous needle tenotomy and PRP injection into the first dorsal compartment, the patient reported improved pain scores and no complications.

OSTEOARTHRITIS

Several studies retrospectively examined the use of PRP and autograft fat injections for the treatment of osteoarthritis. Loibl et al[3] performed a pilot study of treatment of trapeziometacarpal (TMC) joint arthritis with PRP injections to determine their effect on pain and functional outcomes. Patients were observed for 6 months after undergoing PRP injections. Ten patients with TMC joint arthritis underwent 2 intra-articular PRP injections administered at 4-week intervals. Patients with more severe osteoarthritis (Eaton-Littler stages 3 and 4) had minimal change in reported outcome measures of pain and *Quick*–Disabilities of the Arm, Shoulder, and Hand Questionnaire (*Quick*DASH) scores, as well as continuously decreasing pinch strength measures. Patients with less severe osteoarthritis (Eaton-Littler stage 2) demonstrated decreased pain and improved *Quick*DASH scores with no change in grip or pinch strength. Loibl et al concluded that PRP injections may be considered an option for managing early-stage TMC joint arthritis. Malahias et al[4] performed a prospective randomized controlled trial (RCT) of 33 patients with clinical and radiographic evidence of TMC joint arthritis. Patients underwent intra-articular injections at 2-week intervals: one group (16 patients)

TABLE 1. Descriptions of Orthobiologic Agents Reviewed in This Article

Orthobiologic Agent	Description
PRP	Plasma with concentrated platelet content. PRP contains growth factors that mitigate inflammation and promote healing and tissue recovery.[28] Platelet-rich plasma is classified based on the presence or absence of leukocytes; activation methods (without activation, activated, or frozen-thawed preparation); absolute number of platelets ($<900 \times 10^3/\mu L$ to $>1,700 \times 10^3/\mu L$); and system used to prepare the PRP (gravitational centrifugation, standard cell separators, or platelet pheresis).[29]
BMPs	Bone morphogenetic proteins recruit osteoblasts to the site of lesions and are osteoinductive in nature. Bone morphogenetic protein-2 and BMP-7 have been successfully genetically engineered to yield promising results.[28] Bone morphogenetic proteins-2 and BMP-7 have anabolic and anti-inflammatory effects.[30]
BMAC	Bone marrow aspirate concentrate originates from the extraction of bone marrow cells.[28] Bone marrow aspirate concentrate has demonstrated *in vivo* generation of hematopoietic cells, fibroblastic reticular cells, and bone.[31]
MSCs	Mesenchymal stem cells are multipotent adult stem cells that are responsible for regenerating and repairing skeletal tissues. These cells are typically extracted from bone marrow and adipose tissue, and are multipotent and capable of self-renewal. MSCs can differentiate into chondrocytes, adipocytes, and osteocytes.[28,29]
Amniotic membrane	Amniotic membrane is the avascular, innermost layer of fetal membranes. The membrane is full-term placental tissue that is treated with antibiotics during collection; it consists of epithelium, basement membrane, and stroma. The basement layer promotes cellular growth whereas the stromal layer reduces inflammation. The membrane has anti-angiogenic and antimicrobial properties.[28]

TABLE 2. United States Food and Drug Administration Approval for Reviewed Orthobiologic Therapies

Orthobiologic Therapy	FDA Approval	Cost
PRP	PRP therapy is not approved and would require 510(k) clearance. FDA 510(k) pathway allows for clearance of products that are the "substantiative equivalent" of prior, cleared products.[32,33]	$300-$2,500 per injection. Average cost is $750 per injection.[33]
BMPs	Recombinant human BMP-2 is approved for use. FDA issued warning for severe complications. Recombinant human BMP-7 is approved for use under the Humanitarian Device Exception.[34,35]	
BMAC	BMAC is approved for usage under FDA Category 1, reserved for non-HCT/Ps.[36]	
MSCs	MSC therapies are not FDA-approved but have been approved in the European Union, Canada, and Australia. There are currently hundreds of clinical trials using MSCs.[36]	
Amniotic membrane	Amniotic membrane products are approved for use under HCT/Ps and the 361 or 351 pathway.[37]	$5,000 per 0.25-μL injection.[37]

FDA, US Food and Drug Administration, HCT/Ps, Human Cells, Tissues, and Cell and Tissue-based products.

underwent PRP injections, and the second group (17 patients) underwent methylprednisolone and lidocaine injections. Both treatment groups had improved pain scores at 3 months; however, at 12 months the PRP injection treatment group demonstrated further improvement in pain scores, whereas the corticosteroid treatment group had worsening pain scores. Similarly, both treatment groups had improved *Quick*DASH scores at 3 months; however, at 12 months the PRP injection treatment group demonstrated further improvement in *Quick*DASH scores whereas the corticosteroid injection treatment group had worsening *Quick*DASH scores. The authors concluded that PRP injections may have more lasting improvements on pain and function compared with corticosteroid injections in patients with mild and moderate TMC joint arthritis.

Haas et al[5] examined the effects of autologous fat graft injection in a review of 99 joints with TMC joint osteoarthritis. Ten patients received bilateral treatment. Patients included demonstrated TMC joint arthritis Eaton-Littler grades 1 to 3. The authors noted that pinch and grip strength for each patient decreased initially, but had returned to a preinjury state within 6 weeks. Follow-up at 12 months indicated that strength was unchanged. Haas et al[5] theorized that transplanted fat tissue may have a buffering and cushioning effect during movement or immunomodulatory and anti-inflammatory effects. An appreciable benefit was shown in 61% of patients at 12 months after surgery, and the authors recommended autologous fat grafting for treatment of TMC joint osteoarthritis.[2] Medina-Porqueres et al[6] published a case report of a pianist with TMC joint arthritis (reportedly Eaton-Littler stage 2) who underwent treatment with 3 PRP injections administered at 1-week intervals. The patient reported decreased pain with return to activities of daily life and improved functional outcome scores. These results were maintained at 12 months. Bohr et al[7] discussed a case of a 62-year-old patient with a history of persistent TMC joint arthritis of the right thumb. The patient had a loss of grip strength and pain radiating from the TMC joint. The patient underwent a cell-enriched lipoaspirate procedure using abdominal liposuction to harvest fat. The lipoaspirates were processed to "increase stromal vascular cellular fraction and reduce non-cellular oil," then injected dorsally into the TMC joint. A *Quick*DASH test score administered 12 months after the procedure was 22, compared with the preprocedural score of 46. The patient also reported decreased pain in the right hand 5 weeks after the procedure.

CARPAL TUNNEL SYNDROME

Several studies have examined the results of orthobiologic agents in the treatment of carpal tunnel syndrome (CTS). Senna et al[8] conducted an RCT including 98 patients with mild to moderate idiopathic CTS. Patients were administered a local steroid injection or PRP injection and then evaluated at 1 and 3 months after the procedure using the visual analog scale (VAS), Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), and electrodiagnostic studies. One month after the injection, the authors found no significant difference in improvement of paresthesias, pain, and BCTQ scores between the experimental and control groups. Specifically, no difference in improvement was noted for motor or sensory conduction parameters. However, at 3 months after the injection, the authors observed a significant difference in improvement in the same parameters, favoring PRP injection over corticosteroids. Malahias et al[9] conducted a double-blind RCT with 91 patients with CTS divided into 2 groups: an experimental PRP injection group and a control saline injection group. Significant differences in *Quick*DASH score success ratios were reported between groups at 12 weeks after the procedure, with a 76.9% success ratio in the PRP injection group and a 33.3% success ratio in the placebo group. Furthermore, 65% of patients in the PRP injection group experienced a final *Quick*DASH score decrease of more than 8.0; only 21% of patients in the placebo group experienced that extent of improvement.

Wu et al[10] described the effects of PRP injection after 6 months in 60 patients with unilateral CTS. The authors described a significant reduction in VAS-Pain score, BCTQ score, and the cross-sectional area of the median nerve, as measured by ultrasound, in the PRP group compared with the use of a wrist orthosis as a control. Güven et al[11] evaluated the impact of PRP injection as an adjuvant to the placement of an orthosis in 40 hands in a total of 30 patients with CTS. In cases of bilateral CTS, each hand was assessed and assigned its own group: only the use of an orthosis versus an orthosis with an adjuvant PRP injection. Both groups had improved BCTQ symptoms and function scores 4 weeks after the procedure. There was a significant difference between the groups favoring PRP injection in terms of decreased symptoms, increased function, and improved electrodiagnostic factors such as distal motor latency and sensory nerve velocity scores compared with the control group. Trull-Ahuir et al[12] conducted a RCT to evaluate PRP injection therapy against platelet-poor plasma after open carpal tunnel release surgery in 50 patients. The authors measured outcomes after 6 weeks via hand grip strength (HGS), days taken off work after the operation, and BCTQ scores. Results indicated that only HGS showed a significant difference in improvement between the 2 patient groups; patients who received PRP regained baseline HGS significantly earlier compared with their platelet-poor plasma counterparts. No other significant differences in parameters, including pain, function, and symptom severity, were noted. The authors recommend PRP for adjuvant treatment of CTS in open release but cautioned against its immediate clinical implementation owing to unknown molecular mechanisms in healing.

Shen et al[13] conducted an RCT evaluating 5% dextrose injection versus PRP injection to treat CTS

in 52 patients. The authors used BCTQ scores, the cross-sectional area of the median nerve measured by ultrasound, and electrodiagnostic assessments to measure outcomes at 1, 3, and 6 months after the procedure. The PRP group demonstrated "significant reductions in BCTQ function at 3 months, distal motor latency at 6 months, and cross-sectional area at 3 and 6 months" compared with the dextrose group. They recommended using both PRP and 5% dextrose to treat moderate CTS.

Kuo et al[14] described the case report of a 56-year-old patient with CTS manifesting as both unbearable pain and paresthesias. The patient experienced 2 months of symptoms in the radial 3 fingers of both hands that was not mitigated by corticosteroid injections. The patient underwent perineural PRP injection and experienced gradual alleviation of pain, paresthesia, and hyperesthesia over the course of 2 weeks. Within 4 months, the patient's electrodiagnostic studies improved, as assessed by increases in conduction velocity and compound muscle action potential amplitudes. The authors supported PRP injection as a viable treatment for patients for whom other nonoperative treatments have failed.

SCAPHOID NONUNION

Several studies reported the results of orthobiologics as adjuvant treatment of scaphoid nonunion. Jones et al[15] published a case report of one patient with a proximal pole scaphoid nonunion who underwent surgical intervention with curettage of the proximal pole, Kirschner wire fixation, and BMP-2. After 12 weeks, radiographs demonstrated bony healing, and a magnetic resonance imaging scan performed 6 years later revealed no evidence of osteonecrosis. They recommended consideration of BMP-2 as an adjuvant for treatment of scaphoid nonunions. Bilic et al[16] examined the effects of BMP-7 (osteogenic protein-1) on scaphoid proximal pole nonunion. They randomized 17 patients with proximal pole scaphoid nonunions to 1 of 3 treatment groups: autologous iliac graft only, autologous iliac graft with BMP-7, and allograft iliac graft with BMP-7. The authors reported that patients who underwent treatment with BMP-7 in addition to autologous iliac graft demonstrated radiographic healing at 4 weeks, compared with 9 weeks in the treatment group without the BMP-7. Computed tomographic scans at 9 months after surgery also demonstrated vascularized proximal poles in the patients in the autograft and BMP-7 and the allograft and BMP-7 groups. They concluded that BMP-7 may have a role in treating scaphoid nonunions and may allow enhanced revascularization of the proximal pole. Ablove et al[17] performed a retrospective study of 4 patients with scaphoid nonunions (3 waist and 1 proximal pole). These patients underwent revision screw fixation and augmentation with BMP-2, without additional bone grafting. All patients went on to heal radiographically at a mean of 53 days after surgery and ultimately returned to all activities of daily life without pain. No complications were noted. The authors concluded that BMP may be a promising adjuvant in the management of scaphoid nonunions.

Rice and Lubahn[18] reported the outcomes of patients who underwent surgical intervention for nonunions of the hand and wrist supplemented with recombinant human (rh)BMP-2. In their series of 27 patients, sites of nonunion included the phalanx, carpus, distal radius, and distal ulna. They found that 24 of 27 patients (89%) achieved union at a mean of 4 months after surgery and concluded that rhBMP-2 did not produce better healing rates compared with previously published union rates of these injuries without rhBMP-2 augmentation. Brannan et al[19] presented a case series reviewing the documented complications for patients who underwent scaphoid nonunion surgery with revision fixation, bone graft, and rhBMP-2. Six cases were reviewed: 2 patients had persistent nonunion, 4 developed heterotopic ossification, one lost functional motion, and one healed without complications. The authors concluded that the use of BMP has potential serious complications, specifically heterotopic ossification.

DISTAL RADIUS FRACTURE

Minimal literature exists regarding the use of orthobiologics as an adjuvant to treat distal radius fractures. Namazi and Mehbudi[20] evaluated wrist range of motion (ROM) and self-reported pain and function scores after injecting autologous PRP in patients who had sustained intra-articular distal radius fractures. They performed a case-control study in which 15 patients from 18 to 50 years of age underwent injection of autologous PRP into the radiocarpal joint after surgical fixation of a distal radius fracture, and 15 patients underwent only surgical fixation. Patients were included if they had a simple intra-articular distal radius fracture of Frykman type 3, 4, 7, or 8. The authors found a statistically significant improvement in patient self-reported pain and functional outcomes at 3 and 6 months in the PRP group; however, there was no statistically significant difference in wrist ROM between the PRP and control groups.

KIENBÖCK DISEASE

Several studies report the use of orthobiologic agents in the treatment of Kienböck disease. Jones et al[21] documented the case report of a patient with Lichtman stage 3 Kienböck disease treated with a first dorsal metacarpal vascularized bone graft with adjuvant BMP placed into the lunate cavity. Two years after surgery, magnetic resonance imaging showed revascularization of areas of the lunate, and at 5 years after surgery, the patient still had resolution of preoperative pain with radiographs that demonstrated no further lunate collapse. The authors concluded that BMP may stimulate vascular ingrowth. Rajfer et al[22] published 2 case reports and an arthroscopic technique using BMP for Kienböck disease. They provided details regarding the technique of inserting BMP via a cannula in addition to an autologous cancellous bone graft into the curettaged lunate cavity through an arthroscopic portal of the wrist. They observed improved postoperative functional and pain outcomes in both cases, and reported that both patients returned to activities of daily life.

TENDON REPAIR

There are few human studies evaluating the use of biologics as an adjuvant in flexor or extensor tendon repair. Leppanen et al[23] studied the use of amniotic membrane allograft as a mechanical barrier to decrease adhesion formation after flexor tendon repair. They anticipated including 10 patients with flexor tendon injuries in their pilot study, with operative treatment including flexor tendon repair and fixation of amniotic membrane allograft around the tendon repair site. However, the study was terminated after unfavorable results in 5 patients, including notable stiffness and repair site failure. The authors concluded that the amniotic membrane allograft does not decrease postoperative inflammation or increase healing after flexor tendon repair.

Several animal studies have been performed evaluating biologics for tendon repair and healing. Studies examining the effect of PRP on tendon repair have shown inconsistent results. Examples include the study performed by Sato et al,[24] who investigated the effects of PRP with fibrin matrix on the healing of rabbit flexor tendons. The authors found no difference in edema or adhesion at the tendon repair sites between the control and PRP with fibrin matrix groups. However, they found significantly increased healing strength at the repair sites in the PRP with fibrin matrix group at 2 weeks compared with the control group, but no significant difference in strength at 3 and 6 weeks between the groups. Kollitz et al[25] examined the effects of PRP on zone II flexor tendon repair sites in a rabbit model. The authors found no significant difference in tensile strength between the PRP and control groups at 2, 4, or 8 weeks, with a nonsignificant but lower tensile strength in the PRP group at 2 weeks. They also found no difference in excursion or ROM between the 2 groups, and indicators of less healing in the PRP group as measured by decreased cell counts and collagen compared with the control group.

Morizaki et al[26] examined PRP and bone marrow-derived stromal cell (BMSC) effects in an *ex vivo* canine model, with 192 flexor digitorum profundus tendons from 12 dogs. They reported that the maximum breaking strength of the healing tendons was significantly increased with BMSC-seeded PRP patches compared with healing tendons without a patch. Although the authors were unable to pinpoint the number of transplanted BMSCs for each tendon repair, they demonstrated the value of using a BMSC patch with PRP in flexor tendon repair in this canine model.

Gelberman et al[27] studied the combined administration of autologous adipose-derived stem cells and recombinant BMP-12 to flexor tendon repair sites in 16 canines. The authors demonstrated that the repair sites did not have adhesions or gap formation after the administration of adipose-derived stem cells and recombinant BMP-12. By assessing gene and protein expression, Gelberman et al postulated that this treatment modulated the postrepair inflammatory response and facilitated healing, affording "accelerated progressive healing during the proliferative stage of tendon repair."

CONCLUSION

Several animal and few human studies have been performed regarding the use of orthobiologic therapies for musculoskeletal conditions of the hand and wrist, with overall inconsistent results and recommendations. In addition, the overwhelming majority of the clinical studies are case series or case studies with low patient numbers, include no comparison groups, and have a limited duration of follow-up. At this time, orthobiologics are not regularly covered by most insurance plans. There are also limited reports on potential donor site morbidity. Additional research is necessary to investigate the short-term and long-term effects of orthobiologic therapies before the widespread use of these agents to treat hand and wrist pathology.

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