The role of biologic in foot and ankle trauma—a review of the literature

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Abstract

Purpose of review The use of biologics in orthopedics is becoming increasingly popular as an adjuvant in healing musculoskeletal injuries. Though many biologics involved in the management of foot and ankle injuries are used based on physician preference, reports of improved outcomes when combined with standard operative treatment has led to further clinical interest especially in foot and ankle trauma.

Recent findings The most recent studies have shown benefits for biologic use in patients predisposed to poor bone and soft tissue healing. Biologics have shown benefit in treating soft tissue injuries such as Achilles ruptures as well as the complications of trauma such as non-unions and osteoarthritis.

Summary Biologics have shown some benefit in improving functional and pain scores, as well as reducing time to heal in foot and ankle traumatic injuries, with particular success shown with patients that have risk factors for poor healing. As the use of biologics continues to increase, there is a need for high-level studies to confirm early findings of lower level reports.

Keywords Platelet-rich plasma · Bone marrow aspirate concentrate · Bone morphogenetic protein · Hyaluronic acid · Scaffolds · Bone allografts · Demineralized bone matrix

Introduction

Trauma of the foot and ankle is a common problem with over 280,000 ankle sprains occurring from 2007 to 2011, according to the National Trauma Data Bank [1, 2]. These injuries predispose patients to developing post-traumatic osteoarthritis (OA). Post-traumatic OA is responsible for up to 78% of OA in the ankle [3]. Furthermore, an estimated 6 million ankle

fractures occur annually with 5 to 10% of those having delayed union or nonunion [4].

Surgical fixation alone results in inadequate treatment of some foot and ankle injuries. Ankle arthrodesis, commonly used in the setting of OA, has failure rates of up to 40% [5]. Additionally, Achilles tendon re-rupture rates after operative treatment is as high as 7% [6]. Osteochondral lesions of the talus (OCL) have fair to excellent results when they are less than 10 mm; however, larger cystic lesions are prone to re-injury and benefit from augmentation [7].

Traumatic injuries, as well as patient medical and social factors, can predispose patients to poor healing, especially with soft tissue injuries. Over the past few decades, biologics have been implemented to aid in the healing process [8]. Biologics, specifically orthobiologics, are biologically viable materials that can be used to improve healing in certain skeletal and soft tissue injuries [8]. The available orthobiologics include a wide array of bone grafts, bone substitutes, growth factors, and scaffolds [8]. These options provide foot and ankle surgeons with tools to supplement traditional operative techniques.

In this review, literature from the previous 5 years was synthesized regarding the use of orthobiologics in foot and ankle traumatic injuries and their long-term complications. To our knowledge, very little has been published on this

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subject and our review provides insight into the most recent developments in the area of biologic use in foot and ankle trauma.

Bone morphogenetic Protein-2 and platelet-derived growth factor

Bone morphogenetic protein (BMP) was first described by Urist in 1965, who discovered a molecule that stimulated bone formation [9]. BMP is a member of the transforming growth factor- β (TGF) supergene family and functions by first attracting mesenchymal stem cells (MSCs) then binding to its receptor, which initiates a cascade of events including activation of Smad proteins that combine and enter the nucleus to stimulate transcription of genes such as: Runx2 to stimulate bone formation [10].

BMP is commercially available in recombinant forms: rhBMP-2 and rhBMP-7 [10]. Due to its ease of use, rhBMP-2 is more commonly utilized in the surgical setting [10]. Manufacturer guidelines call for BMP to be soaked on an absorbable collagen sponge at a concentration of 1.5 mg/ml, which is then applied at the site of the injury [11].

Currently, the Food and Drug Administration (FDA) approves the use of rhBMP-2 for spinal fusions, acute trauma of the tibia, and head and neck bone grafting procedures [12•]. The use of BMP in foot and ankle injuries is off-label, but there are studies indicating a role for BMP in ankle arthrodesis and bony non-unions [10–13]. Though no recent study currently focuses solely on its use in foot and ankle trauma, BMP does serve as an adjuvant during treatment of the complications of trauma, such as arthritis and non-unions [10–14].

Rearick and colleagues showed a 92% union rate after patients underwent arthrodesis or fixation for prior foot and ankle fracture non-unions and had an average time to union of 111 days [11]. In another study, Fourman et al. showed similar rates of union, 92% in the treatment group with adjuvant rhBMP2 vs 53% in the control group [13]. Lucas et al. showed that adding BMP-2 to an allograft can reliably increase the chances of progressing to union after a primary tibiocalcaneal arthrodesis [14].

Another growth factor used in foot and ankle injuries is platelet-derived growth factor (PDGF), which attracts mesenchymal stem cells (MSCs) to the site of injury and stimulates expression of angiogenic factors to facilitate healing [15]. PDGF is used alongside beta-tricalcium phosphate granules (β -TCP) as a method of delivery to the injury site, a mixture that includes a 0.3 mg/ml concentration of PDGF [15].

Recent studies have shown PDGF to be comparable to autologous bone grafts in terms of radiographic unions, pain scores and complication rates [16]. In a level I study, Daniels and colleagues demonstrated an 84% fusion rate in ankle and hindfoot arthrodesis 24-weeks postoperatively, significantly higher than the 65% fusion rate seen in

patients treated with autografts ($p < 0.001$) [17]. These studies collectively show that PDGF is a reasonable alternative to bone grafts in patients that would benefit from hindfoot and ankle arthrodesis [16, 17].

Based on these recent studies, rhBMP2 has a role in the management of foot and ankle fracture non-unions as well as for patients with post-traumatic ankle osteoarthritis who require arthrodesis for relief of their symptoms. PDGF also has a role in the management of post-traumatic ankle osteoarthritis and has been shown to be comparable to the standard bone grafts during hindfoot and ankle arthrodesis.

Hyaluronic acid/scaffold-based therapy

Scaffolds and hyaluronic acid therapy are used primarily to target disease processes that affect articular cartilage, such as OCLs and OA of the ankle [18–30]. OA of the ankle is primarily post-traumatic (70%), and as such, is relevant when discussing foot and ankle trauma [18].

There are various types of scaffolds used to treat foot and ankle injuries which include the following: autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), autologous matrix-induced chondrogenesis (AMIC), and matrix-induced stem cell transplantation (MAST) [19–28]. Scaffolds should be designed to mimic an environment suitable for chondrocyte growth and differentiation, which ensures that the scaffold's therapeutic effects are realized [31–33].

ACI and MACI are two-stage scaffolds that require donor site morbidity when cartilage is taken from a healthy part of the body, cultured and then re-implanted at the site of injury [20, 21]. These scaffolds have demonstrated favorable results when used to treat OCLs. Kwak et al. reported a significant increase in American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scores, from 50.1 to 85.9; and in another study reported by Giannini et al., 57.2 pre-operatively to 92 at 14.5 months post-operatively [20, 21].

AMIC and MAST are single-stage scaffolds involving implantation without the need for cells to be cultured [19, 23–25, 28]. The literature on AMIC shows that it can significantly improve AOFAS scores post-operatively and reduce pain in patients with OCLs [19, 22–24]. MAST in the literature showed improved clinical scores and improved pain scores post-operatively in a study by Richter and Zech; and cell-free scaffolds have also shown significant improvements in AOFAS score after surgery [25, 26, 28].

Hyaluronic acid (HA) is necessary to maintain proper, well aligned joint space and is secreted by the surrounding cells, i.e., synoviocytes, chondrocytes, and fibroblasts [29, 30]. Synthetic HA can be delivered via intra-articular injection primarily to help treat patients with OA [29, 30]. In a study by Shang, synthetic HA injection following microfracture resulted in significantly improved outcomes in terms of cartilage

thickness, T2 index, AOFAS scores, and VAS scores compared to the over the microfracture only group [29]. In a prospective study by Murphy et al., AOFAS scores were significantly improved from 48 to 78 [30] after 6 months of follow-up [18]. In a level I study for the treatment of OCLs, both platelet-rich plasma (PRP) and HA treatment groups had improved AOFAS and VAS scores post-operatively; however, PRP had a more significant impact on AOFAS scores [30].

Bone allografts and bone graft substitutes

Autologous bone grafts have traditionally been the gold standard for addressing bone loss after acute fractures. However, donor site morbidity and limited graft volume have led to the use of bone allografts and bone graft substitutes. Allografts are utilized based on the type of bony defect to provide structure and/or to occupy bony lesions (cortical, cancellous, cortico-cancellous). Bone graft substitutes are synthetic or biologic substances implanted into bone defects as another alternative to autologous and allogenic bone grafts [8]. While synthetic materials do not carry the risk of host reaction to foreign antigens, they are limited in their osteogenic and osteoinductive properties compared to standard bone grafts. Synthetic materials provide an osteoconductive scaffold for the proliferation of osteoprogenitor cells to promote the growth of new bone. The most commonly used bone graft substitutes today are calcium sulfate (CS), calcium phosphate (CP), and tricalcium phosphate (TCP). In recent foot and ankle trauma literature, the use of bone grafts and substitutes have mainly focused on calcaneus fractures [34–38•].

Intra-articular calcaneus fractures are often comminuted, involving the collapse of the subtalar joint and loss of calcaneal height. The goal of fracture fixation is to restore Bohler's angle, which usually requires open reduction internal fixation (ORIF) [34]. Usage of bone grafts to fill in the bony void has been controversial due to the theoretical increase in infections in a procedure that already carries a high infection risk due to wound complications [35]. In a study comparing ORIF of Sanders II, III, and IV calcaneal fractures using the lateral extensile approach, with and without cancellous allograft, the authors found no significant difference in functional scores between the two groups, although there was a significant loss in postoperative calcaneal height and Bohler's angle in the non-bone graft group compared to the bone graft group at 1-year postoperatively [36]. As such, the decision to use grafts for these fractures is based on surgeon preference. Furthermore, infections occurred in both study groups [36].

Minimally invasive bone graft techniques have been studied to reduce wound complications such as infections [37]. Feng et al. randomized patients with Sanders II and III intra-articular calcaneus fractures to percutaneous reduction cannulated screw fixation with calcium sulfate cement grafting (PR + CSC) and plate fixation through a minimally invasive sinus

tarsus approach (MISTA). They found that both groups had equivocal functional scores and restoration of Bohler's angle, Gissane's angle, calcaneal height, and width [37]. Notably, the PR + CSC group had significantly less postoperative wound-related complications at 7.1% compared to 28.9% in the MISTA group ($p = 0.010$) [37]. However, the wound complication rate in this study was higher than other studies which had shown little or no wound complications when MISTA was implemented [39, 40]. Biggi et al. describe the use of balloon-assisted augmentation using calcium phosphate, like kyphoplasty for vertebral compression fractures, as a newer, less invasive method for delivering bone grafts in treating calcaneus fractures [38•]. This “minimally invasive percutaneous calcaneoplasty” technique used in Sanders II and III fractures was able to restore Bohler's angle from a mean pre-operative value of 9.91° to a mean postoperative value of 22.97° after 2 years of follow-up with no infections noted [38•]. Another group used this technique in treating osteoporotic calcaneal insufficiency fractures and found complete reduction in pain at 1-year follow-up. While infection remains a risk with operative management of calcaneus fractures, restoration of anatomic Bohler's angle predicts functional recovery and newer less invasive methods of incorporating bone allografts and substitutes may allow for surgical success with fewer complications.

Platelet-rich plasma (PRP)

Platelet rich plasma (PRP) is an autologous concentrate of platelets, containing PDGFs, cytokines, and a variety of other growth factors that help stimulate healing. PRP has been used as an adjunct to treat many orthopedic injuries. It is obtained from peripheral venous blood, prepared and administered at the site of injury.

Depending on the system used, the volume of venous blood may vary. The drawn blood sample is centrifuged into these separate components: platelet-poor plasma, red blood cells, and PRP. The PRP concentrate is isolated, usually less than 10 mL depending on the initial blood volume, and used for injection into the area of treatment with or without local anesthesia [41]. The injection can be administered in an outpatient setting or as an adjunct during surgical fixation. Due to its autologous nature, it has an excellent safety profile with minimal side effects.

Acute Achilles tendon ruptures are one of the more common tendinous injuries and PRP has been studied as an adjunct to both conservative and surgical treatment. Using a rat model, PRP was shown to stimulate tendon-derived stem cells (TDSCs) and have stimulatory effects on Achilles tendon healing by improving the macroscopic and histologic appearance of the tendon; however, in humans, the benefit is less clear [42]. A study comparing functional outcomes of patients with Achilles tendon ruptures treated conservatively with and

without PRP injections showed no difference in plantarflexion strength, pain, function, and range of motion at any time point [43]. A prospective randomized controlled trial comparing surgical repair of acute Achilles tendon ruptures, with and without PRP injection, into the paratendon showed improved function and pain scores and increased calf strength in the PRP group at short-term follow-up (within 6 months), but no difference at long-term follow-up (1–2 years) [44]. While PRP has no conclusive benefit in nonsurgical management of acute Achilles tendon ruptures, it may have a perceived short-term benefit in patients treated with surgical repair.

Recently, PRP has been purported for use in treating ankle sprains. Rowden et al. performed a randomized double-blind placebo controlled study comparing the use of PRP versus placebo saline injection in patients presenting to the emergency department with negative findings for a severe ankle sprain, which were defined as the inability to walk, diffuse tenderness and swelling [45]. Patients were randomized to PRP or placebo saline injections to the area of ligamentous injury based on ultrasound or at the point of maximal tenderness [45]. Patients were followed for 1 month and no difference was observed in functional scores or pain between the two groups [45]. This study had a heterogeneous population with short-term follow-up and no specific rehabilitation protocol [45]. However, future studies with more homogeneous patient populations may be better equipped to detect an effect. Laver et al. described the use of PRP in treating college level elite athletes with high ankle sprains or syndesmotom injuries. Athletes received either an injection of PRP to the torn anterior inferior tibiofibular ligament (AITFL) or no injection, in addition to rehabilitation and return to play protocol [46]. Compared to the control group, athletes that received PRP were able to return to play sooner (41 vs 60 days), had less pain and had no recurrence in either groups at 2 years [46]. Similarly, rugby players with syndesmotom injuries and treated with PRP injection into their AITFL were found to have shorter return to play time compared to a historically similar cohort not treated with PRP [47]. Elite athletes, however, tend to be a highly motivated group of patients, and prone to selection and treatment bias, but these studies suggest that PRP may have benefit in aiding conservative management of soft tissue injuries in select populations.

The use of PRP as an adjunct to fracture healing has not been widely studied, especially in the foot and ankle literature. Rat models have shown that PRP may aid fracture fixation histologically compared to fracture fixation alone; however, this result has yet to be shown conclusively in human models [48]. PRP has also been studied as an adjunct in treatment of non-unions. A randomized, controlled double-blind trial showed that PRP in addition to autologous bone graft had significantly shorter healing time, higher rates of union, and less pain when treating non-unions of long bones compared to

autologous bone grafting and saline, although there may be a higher infection rate [49]. In foot and ankle trauma, the only recent study that discussed use of PRP combined with bone marrow aspirate concentrate as an adjunct to demineralized bone matrix (DBM) that was injected into fracture sites of patients with high surgical morbidity treated with Ilizarov frames [50]. This study showed that patients treated with DBM in addition to BMAC and PRP had significantly faster healing times than patients treated with DBM alone; however, this effect could not be isolated to that of PRP alone [50]. More research is needed to study whether PRP may expedite healing times especially in foot and ankle trauma where faster healing allows for faster return to weight bearing and faster return to function for patients.

Bone marrow aspirate concentrate

Bone marrow aspirate concentrate (BMAC), is a biologic concentrate derived from harvesting mesenchymal stem cells (MSCs). BMAC has been used as an adjunctive treatment to augment bone, cartilage, and soft tissue healing. The harvest site is important to optimize retrieval. The iliac crest is a common source for the aspiration of MSCs from the bone marrow. Successful retrieval results in a sample that contains MSCs, hematopoietic stem cells (HSCs), bone morphogenetic proteins, growth factors, and other progenitor cells [51, 52]. Both MSCs and HSCs can mature into osteogenic progenitors when induced by the appropriate growth factors and induction proteins [51].

Hyer et al. compared three harvest sites (the distal tibia, calcaneus, and the iliac crest) and found that the calcaneus and the distal tibia had a much lower concentration of MSCs compared to the iliac crest [53••]. Pierini also conducted a study to determine an appropriate donor site and found that the posterior iliac crest had a mean number of MSCs that was 60% greater than the anterior iliac crest, which is currently the gold standard for orthopedic trauma and lower extremity procedures [54••]. The method of harvesting is also critical to obtaining an adequate concentration, which varies depending on the fracture site. One study found that an increased concentration of MSCs is obtained when a smaller syringe (10 vs 50 mL) is used [55]. They also found that the first 10% of volume retrieved in the 10 mL syringe had a higher concentration of MSCs compared to the first 10% of volume retrieved in the 50 mL syringe [55].

There has been increased popularity in the use of BMAC for conservative treatment and as an operative supplement in the management of foot and ankle injuries, with strong evidence in animal investigations to support the utilization of BMAC to aid in bone healing. However, there is a paucity of literature that details the clinical impact of BMAC, particularly in the traumatic setting when several growth factors are intrinsically released during the healing cascade. In a study by Hemigou et

al., diabetic patients with a nonunion of their ankle fractures were treated with BMAC and compared to a cohort treated with standard bone iliac crest autograft [56]. BMAC promoted progressive healing of the nonunion in 82% of subjects, compared to only 62% in the control group [56]. Additionally, the BMAC group had significantly less complications including infection, skin necrosis, need for amputation, and issues with the donor site [56]. In another study, Hernigou et al. showed that patients with an infected nonunion have lower rates of infection recurrence and bone resorption of the graft when treated with adjunctive bone marrow granulocyte precursors in conjunction with cancellous bone graft [57]. Among those in the BMAC treatment group, 95% progressed to successful healing after an infected-related nonunion, compared to only 40% of the control group that was treated with a single-stage debridement and iliac crest bone graft [57].

Although early results related to the management of non-unions have been promising, the exact role of BMAC administration in orthopedic trauma remains an area of uncertainty. Given the current literature, BMAC may be indicated in cases that have a higher risk of progressing to delay union or nonunion. This includes patients that have diabetes, high BMI, smokers, or compromised blood flow. In such patients, the advantages of promoting progression to union may outweigh potential and/or unknown risks associated with the harvesting and long-term effects.

Demineralized bone matrix

Demineralized bone matrix (DBM) is a popular alloimplant, evidenced by its utilization in over 20% of bone grafting procedures worldwide. Although the use is widespread, limited evidence exists regarding the role of DBM in foot and ankle trauma. Among the few studies reported, there is inconsistency regarding DBM product type, application, and evaluation.

Nonetheless, there is some evidence that DBM can be beneficial in foot and ankle trauma [58–60]. In a study by Galli et al., the efficacy of 12 medial malleolar osteotomies with DBM subchondral bone grafting was evaluated as treatment for medial cystic, full thickness OCLs following failed microfracture. Pain scores were shown to be significantly reduced between 6 and 24 months. In this study, disability was recorded as pain scores while ambulating up and down stairs, as well as walking for less than four blocks [58].

Lareau and colleagues assessed the efficacy of intramedullary screw fixation with BMAC and DBM in the treatment of acute zone 2 and zone 3 Jones fractures in NFL players [60]. The study showed a 100% return to play (RTP) rate with an average time to RTP of 8.7 weeks [60]. In an earlier study by Hunt and Anderson, there was a similar RTP rate; however, the time to RTP was 12.3 weeks [61]. These findings suggest that DBM and BMAC have a benefit

compared to operative treatment alone for acute zones 2 and 3 Jones fractures in athletes.

Discussion

The use of biologics in foot and ankle trauma is a relatively new and developing field. The main purpose of biologics is to provide an adjunct to stimulate bone and soft tissue healing. Some biologics, such as bone morphogenic protein and platelet-derived growth factor, are molecules that stimulate transcription of proteins to stimulate bone healing. The use of these molecules has been more studied in other areas of orthopedic trauma, such as treatment of tibial fractures and tibial non-unions but can be applied similarly in foot and ankle trauma [10, 16]. While the literature is limited on the use of BMP and PDGF in primary fracture care, its role in increasing the rate of hindfoot and ankle fusion in the setting of trauma patients is promising [14, 16, 17]. Other biologics, such as bone allografts, bone substitutes, and demineralized bone matrix, provide physical material similar to bone to provide structural support to fill in bony voids and they may also have osteoconductive and osteoinductive properties to aid in achieving bony union. While increasing infection rates may be a concern with the use of bone allografts and substitutes, especially in the setting of calcaneal fractures, newer less invasive methods of delivery can help lower infection rates, while also providing material that helps restore bony anatomy and improves function [37, 38]. Platelet-rich plasma and bone marrow aspirate concentrate are two types of concentrated autologous materials that provide a variety of molecules that help stimulate growth and healing. The main advantages of using PRP and BMAC are their autologous nature, minimal donor site morbidity, and excellent safety profile. PRP has been studied more in the treatment of soft tissue injuries, such as Achilles tendon and ankle ligamentous injuries [42–47]; whereas BMAC is utilized more often in bony injuries, such as ankle fractures [56]. The literature describing the overall benefit of these materials is not clear as there is no standardized method of administration described. This is an area that requires some attention as optimal treatment protocols are being explored. Lastly, cartilage damage to the talus is a significant sequelae of ankle trauma and methods to help prevent or prolong the onset of post-traumatic arthritis is significant to improving patient outcomes. Various types of scaffolds have been described that can be implanted into cartilage defects with significant improvements in AOFAS scores [20, 21]. Like its use in treating degenerative arthritis of the knees, hyaluronic acid can also be injected into the ankle to help with pain control and function and is useful in nonsurgical management of ankle arthritis [29, 30]. While there is a wealth of biologic

materials available to be used in both surgical and nonsurgical management of foot and ankle trauma, more studies are needed to document the effects of these materials and how to standardize their use in patient care.

Conclusion

The use of biologics in foot and ankle trauma continues to be of great interest. As medical advances arise, there remains a great need for high-level research to improve our understanding of the indications and long-term effects of biologic augmentation in the management of foot and ankle orthopedic traumatic injuries. The current literature regarding biologic use in traumatic injuries, as well as their long-term complications, shows promising early results. As the literature grows, we expect further research to determine the optimal dosage, method of retrieval, frequency, and timing for adjunctive treatments to better inform surgeons' clinical decision-making in foot and ankle trauma.

Compliance with Ethics Standards

Conflict of interest All authors declare that they have no conflicts of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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