

Orthobiologics-Today

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Abstract

Orthobiologics is a newer science that has biologic-based therapies for treatment of various hip, knee, ankle and shoulder pathologies. It involve biological sources which promote and accelerate bone and soft tissue healing and based on theoretical advantages in focal chondral defect, osteoarthritis, AVN hip, plantar fasciitis and various tendinopathies. Strong evidence which support the use of biologic agent such as hyaluronic acid, platelet rich plasma bone marrow aspirate concentrate, largely remain absent from the literature. This article review the existing literature on most commonly employed biologic agent for the different knee, hip, and ankle pathologies. There was a lack of clinical evidence for various treatment strategies; therefore we suggest that there is a need for comparative studies in future.

Keywords: Orthobiologics, Hyaluronic acid, platelet rich plasma, Bone marrow aspirate concentrate; Adipose derived stem cells, Osteoarthritis

Introduction:

Orthobiologics involve tissue healing and biological restoration by harnessing the regenerative potential within the body's own cells and redirecting their use for accelerated healing in damaged or diseased tissues. Many cellular therapies are evolving as a bridge between conservative non-invasive options and invasive surgical treatments. Orthopedists are increasingly looking to biologics and cellular therapies to improve patient care. There are two primary reasons for this: 1) to improve the efficacy of implants and surgical procedures; and 2) to reduce or eliminate the need for invasive surgery. The market for biologic and cellular therapies in orthopaedics is commonly referred to as the Orthobiologics and is made up of a select group of products that range from recombinant growth factors to synthetic

matrices and bone void fillers [1].

Generations of Orthobiologics: -

Currently, there are 4 generations of orthobiologics including: Hyaluronic acid (HA), platelet-rich plasma (PRP), bone marrow concentrate (BMC), and adipose-derived mesenchymal stem cells (aMSC). Although the current landscape of orthobiologics can be classified by 4 generations, the field as a whole is in the preliminary stages.

Continued research and collaboration is needed to expand our understanding of these treatments and shape its future direction [2].

A. Hyaluronic Acid (HA) :-

First-generation biologics consisted of visco-supplementation for joint arthritis, in the form of HA.

Viscosupplementation involves the intra-articular injection of HA, a sticky viscous glycosaminoglycan, which can provide lubrication and shock absorbency for a damaged joint [3], as well as pain reduction and functional improvements [4]. This form of biologic therapy has illustrated significant results for patients experiencing painful OA.

Given the better safety profile than continuous NSAID use for pain control, especially in elderly populations with more susceptibility to systemic effects, HA is viewed as a viable treatment alternative in OA [5]. Furthermore, HA was shown to exhibit therapeutic effects at 4 weeks, with peak efficacy at 8 weeks and even illustrated residual therapeutic results at 24 weeks in a large meta-analysis conducted by Bannuru et al. [6]. However, this first-generation biologic represented a non-native form of cellular therapy, as the injectable forms of HA on the market are produced from sources outside of the body, such as bacteria, avian and synthetic origins.

B. Platelet Rich Plasma (PRP):-

PRP was first used for open heart surgery in 1987 but has since emerged as the 2nd generation of orthobiologics for musculoskeletal pathology. PRP is extracted from a patient's own Blood. Venous blood is drawn from the patient and centrifuged in order to separate the blood into multiple layers, including the buffy coat, which contains the largest

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concentration of platelets. The buffy coat is removed from the processed venous blood and re-injected into various treatment areas [7].

Growth Factors In PRP: The proposed therapeutic benefit of PRP is based in its ability to stimulate an inflammatory cascade and initiate a healing response through release of healing proteins called growth factors from its alpha granules, including transforming growth factor beta (TGFbeta), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), epidermal growth factor (EGFs) and fibroblast growth factor (FGF)-2. More recent theories of PRP's mechanism suggest that intra articular application may potentially alter the entire joint environment via the signalling cascade, creating a more advantageous inflammatory environment for healing [8].

Classifications of different platelet concentrates into four broad categories depending on leukocyte and fibrin content alone

1. Pure platelet rich plasma
2. Leukocyte and platelet rich plasma
3. Pure platelet rich fibrin
4. Leukocyte and platelet rich fibrin

Applications of PRP: Most of the research for PRP consists of heterogenous, small case series, however some larger RCT have demonstrated its use in areas such as chronic tendinopathies [9] and knee OA [10]. In addition, its application for facet mediated low back pain and degenerative disc disease have also started to be researched[11].

PRP In Knee Pathology:-

PRP in OA and focal chondral defect of knee:- Intra-articular PRP injections for the treatment of focal chondral defects and early mild to moderate OA have been reported to reduce pain, while also improving ROM and quality of life

[12]. A study of 261 patients with symptomatic OA of the knee, following intra-articular infiltration of PRGF, reported improvement in the function and quality of life measured by osteoarthritis-specific and general clinical assessment instruments at 6-month follow-up [13]. These findings suggest PRGF is a potential therapy for OA. [14] in a study of 91 patients observed that treatment with PRP injections reduced pain and improved knee function and quality of life with short-term efficacy; the greatest effect was observed at 12 months but diminished by 24 months.

PRP in ACL reconstruction: In vivo anterior cruciate ligament (ACL) healing following PRP treatment has also been studied, with some studies reporting improvement in ACL graft healing as measured mechanically or with MRI [15,16]. Conversely, other studies have demonstrated no beneficial effects on ACL healing when examining the same parameters [17,18].

PRP in TKA: A retrospective case control study has described the effect of autologous platelet gel applied to exposed tissues, synovium and the lining of the wound at closure following TKA [19]. Interestingly, the patients receiving platelet gel during surgery had less postoperative blood loss as measured by differences in preoperative and postoperative haemoglobin on day 3, lesser narcotic requirement and a higher range of motion prior to discharge than their control counterparts. Everts et al [20] obtained similar results in their study, where autologous platelet gel and fibrin sealant application during unilateral TKA was found to help reduce the peri-operative incidence of blood transfusions.

PRP In Hip Pathology: One comparative study was found assessing the effect of injecting PRP into the hip joint following arthroscopic surgery for labral tears[21]. After a follow-up period of 2 years the pain level in the

PRP treated patients was higher than the control group; however, there were no differences in hip function scores or rate of revision surgery. IN cases with advanced stage AVNFB (stage IIB and IIC), Autologous bone graft mixed with PRP was installed into the necrotic area after debridement. All patients at 14 months FU reported a significant reduction in pain intensity by >60% on a VAS scale and a return to activities of daily living by 5 months [22].

PRP in foot and ankle pathology:

PRP in the treatment of chronic Achilles tendinopathy:-Krogh et al. [23] found no significant difference between PRP and saline group at 3 months with regard to primary or majority of secondary outcomes in tendoachillis pathology]. Boesen et al. [24] observed that PRP group showed significant benefit over placebo in all outcome measures at 6, 12, and 24 weeks of follow-up. Athletes receiving PRGF recovered their ROM earlier, showed no wound complication, and took less time to resume gentle running and training activities [25]. On the contrary, a RCT of 30 patients with surgical repair of Achilles tendon reported no additional benefit of PRP over standard treatment [26].

PRP in plantar fasciitis: Kumar Jain et al. [27] compared single injections of PRP or corticosteroid in patients with chronic plantar fasciitis and observed no significant difference in improvement between the two groups. Acosta-Olivo et al. [28] demonstrated similar results showing that PRP had an efficacy equal to that of corticosteroids.

PRP in osteochondral lesions of the talus :- Gormeli et al. [29] performed a RCT comparing patients treated with microfracture surgery alone versus microsurgery combined with PRP. They found that both groups had significantly improved clinical outcomes, but the PRP group had superior outcomes to the microfracture-only group. MeiDan

et al.[30] compared clinical and functional outcomes following 3 intra-articular injections of either PRP or HA. He found that PRP treatment lead to significantly better outcomes in pain and function compared to HA at 28 weeks. The evidence for PRP in the treatment of osteochondral lesions of the talus is promising, but further studies are needed to evaluate preparation, protocol, safety profile, and long-term results before a definitive conclusion can be made.

PRP in ankle osteoarthritis: Repetto et al. [31] and Fukawa et al.[32] evaluated patients with symptomatic OA after PRP injections. They found significant improvements in pain, function, and patient satisfaction after treatment. The maximal pain reduction did occur at 12 weeks after which pain began to trend toward baseline levels but remained significantly improved. Given the paucity of current evidence on PRP in ankle OA, no definitive conclusion can be made about its benefit at this time.

PRP in wound healing: Ahmed et al. [33] compared PRP platelet gel applied twice weekly to daily antiseptic ointment dressing changes in the treatment of diabetic foot ulcers. They found that PRP had significantly better healing rate and lower wound infection. Martinez-Zapata et al.[34] performed a Cochrane Database systematic review and concluded that PRP may improve healing of diabetic foot ulcers but cautioned that this recommendation was based on low quality evidence. Kane et al.[35]evaluated the use of PRP in wound healing after total ankle arthroplasty and found no significant difference in wound healing complications between two groups.

PRP in Shoulder and Elbow:

PRP in Epicondylitis: A Dutch RCT comparing the effectiveness of leukocyte enriched PRP to standard corticosteroid treatment for lateral

epicondylitis found the former reduced VAS pain scores and DASH outcome scores by 25% [36]. Another independent study found a single platelet-rich plasma injection improved pain and function scores in 29 patients who failed to improve with 6 months of corticosteroid treatment [37].

PRP in Rotator cuff repair: Rendelli and colleagues [38] found in their study that pain and function score are significantly higher in the treatment group than the control group at 3 months after surgery. However, no long-term noticeable differences were noted after 6 months. Follow up MRI showed no significant difference in the healing rates of the rotator cuff tear in both groups. On the contrary, Castricini and colleagues [39] in their RCT did not find the use of autologous platelet-rich fibrin matrix beneficial for augmentation of a double-row repair of small or medium rotator cuff tears.

PRP in Sub-acromial decompression: A study of 40 patients evaluating the effect of platelet leukocyte gel produced from PLRP on the postoperative recovery of patients undergoing open sub-acromial decompression observed faster recovery, earlier return to daily activities and decreased pain medication requirement in the platelet-leukocyte gel-treated group [40].

Conclusion of PRP as Orthobiologics:-

Available data suggest that, the clinical application of PRP in arthritis and bone repair is controversial. PRP is most helpful in chronic tendinopathies, such as tennis elbow and patellar tendonitis, as well as certain revision surgeries with compromised healing milieu. Pooled results from six RCT from different clinical applications of PRP in a recent meta-analysis[41] found no significant benefit up to 24 months with the use of PRP. The observed trend towards benefit with PRP use still remains questionable.

C. Bone Marrow Concentrates In Orthobiologics(BMAC): -

The 3rd generation of Orthobiologics is bone marrow aspirate concentrate (BMAC), which consists of a milieu of mesenchymal stem cells (MSCs), hematopoietic cells, platelets, and cytokines noted for possessing anti-inflammatory, immunomodulatory, and chondrogenic properties [42]. Adult BMSCs have two primary functions: (1) To differentiate into distinctive end-stage cell types such as bone, cartilage, and tendon; and (2) To secrete bioactive macromolecules that are both immunoregulatory and regenerative. Procurement of BMC includes aspiration of bone marrow from the patient, usually at the posterior superior iliac crest under fluoroscopic or ultrasound guidance. In a similar manner to PRP, the aspirate is then centrifuged, and specific layers are extracted for injection.

BMAC In Knee Pathology:

BMAC in full thickness chondral lesion of knee: Enea et al. [43] found significant clinical improvement. Cartilage macroscopic assessment at 12 months revealed all repairs appeared almost normal. Post op MRIs (6-9 months out) all showed reconstitution of original cartilage. Gobbi et al [44] found significant improvement at follow up across all measures. Single lesion and smaller lesions had better improvement. MRI showed greater hyaline-like tissue in all patients. Krych et al [45]. observed that distal femur BMAC and PRP groups had superior cartilage infill. BMAC demonstrated mean T2 value closer to that of superficial hyaline cartilage .

BMAC in osteochondral defect of knee: Buda et al. [46] found good clinical outcome and osteochondral regeneration in knee on MRI and biopsy. Gobbi et al.[47] compared the clinical outcome in knee with OCL which are treated with microfracture and HA-BMAC. They found that

Microfracture group- 64% normal/nearly normal according to IKDC objective score at 2 yrs. and declined to 28% at 5 yr. HA-BMAC group. - 100% normal/nearly normal objective IKDC at 2 yrs. 100% at 5 yrs. for all.

BMAC in knee OA: Centeno et al.[48] found that after BMAC injection, significant positive results occur with treatment for all pain and functional metrics. Higher cell group reported lower post treatment numeric pain scale values. No significant difference detected for other metrics. Haleem et al. [49] found, All patients had statistically significant improvement at 6 and 12 months. High BMI (> 27.5) and large lesion (> 5.4 cm²) had significant prediction of poor clinical and arthroscopic outcomes. Shapiro et al. [50] found, OARSI and VAS decreased significantly from baseline at 1wk, 3 month, 6 months, no difference in pain relief.

BMAC in AVN hip: A recently published long-term outcome (FU 8 and 18 years) reported 17.6% conversion to THA. The rest (82.4%) had significant improvement in the HHS at the end of the follow-up [51]. They also reported a complete resolution of the disease in 12.9% of patients (all were ARCO stage 1) and a reduction in the necrotic lesion size in the rest of the hips (69.5%). Gangji et al. [52], performed a RCT study comparing the efficacy of CD+ BMAC versus CD alone. With FU of 60 months they observed significant improvement in clinical status in the Group receiving BMAC. Sen et al. [53] conducted a RCT comparing CD alone versus CD and autologous BMAC with follow up of 24 months and observed significant improvement in mean HHS at 24 months in FICAT stage I & stage II patients after using CD with mesenchymal stem cells, but further observed that in AVN Ficat stage I

patients, the benefit of addition of stem cell was not that very marked.

BMAC in OCD of talus: Buda et al.[54] compared 2 group with OCD talus treated with (1) Autologous chondrocytes implantation; and (2) BMAC at FU of 48 months. Both Groups had similar results at 48 months. Return to sport was slightly better with BMAC. Giannini et al.[55] found statistically significant improvement in mean AOFAS scores postoperatively ($P < 0.0005$) in patient with OCL of talus treated with BMAC.

BMAC in Tendo Achilles healing: Stein et al.[56] studied 28 patients with open TA repairs with BMAC with a mean follow up pf 29.7 months. All patients achieved good or excellent outcomes postoperatively by attaining functional use or return to sport. Overall 92% patients returned to their preferred sport successfully at 5.9 ± 1.8 mo. All patients were able to achieve a ROM of neutral dorsiflexion or greater and were able to successfully perform a single-limb heel raise at final follow-up.

BMAC in fracture non-union/delay union: Bastos Filho et al. [57] used BMAC in Tibia/femur non-union and observed bone consolidation to be obtained in all the patients. Bone callus observed in the radiographic average 13.8 wk in group without processing. Desai et al. [58] studied 49 patients with tibial nonunion using BMAC injection with DBM and/ or rhBMP-2. The follow up was made until radiographic union or another procedure was performed and found no difference in healing rate between patients with fracture gaps greater than 5 mm. Garnavos et al. [59] observed sound union obtained in all cases of Humeral shaft delayed union from 12 to 20 wks. after the operation. At final follow-up, all patients had regained a satisfactory range of shoulder and elbow motion.

BMAC in rotator cuff repair of

shoulder:- Hernigou et al. [60] study Rotator cuff healing in patient (n = 45) received MSCs during repair. n = 45 matched control group of 45 patients who did not receive MSCs. Follow up: 3, 6, 12, 24 month and 10 yr. 45/45 repairs with MSC augmentation had healed by six months vs 30/45 repairs without MSC treatment by 6 mo. Intact rotator cuffs were found in 39/45 patients in the MSC-treated group, but just 20/45 patients in the control group. Mazzocca et al.[61] found, no statistically significant difference in the Single Assessment Numeric Evaluation score, ROM measures or postoperative strength measures between groups (Rotator cuff repair with or without BMAC).

Conclusion of BMAC as

Orthobiologics:-

The current literature demonstrates the potential benefits of utilizing BMAC for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. Although several studies evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for each tissue environment.

D. Adipose Derived Stem Cell in Orthobiologics (ADMSCs):-

The newest and 4th generation of orthobiologics is known as lipoaspirate/adipose derived mesenchymal stem cells (aMSCs). Lipoaspirate is obtained in larger amounts with less invasive techniques via local anaesthesia and vacuum assisted lipectomy to the posterior superior buttock or lateral thigh or abdomen. Similar to BMC, processed lipoaspirate has illustrated chondrogenic, osteogenic, adipogenic, myogenic, and neurogenic differentiation in the presence of certain induction factors[62,63]. Some research has illustrated that aMSCs actually possess larger total numbers of MSCs; however data is mixed as to whether aMSCs

have equivalent osteogenic potential as BMC [64,65]. However significant research is need in this generation of orthobiologics. Adipose Derived Stem Cell in OA Knee:- Centeno et al.[66] had Compare 2 groups (1) BMAC+ PRP vs (2) BMAC + PRP + adipose graft. Found no difference between groups. Addition of adipose graft did not provide a detectible benefit over BOAC alone. Koh et al. [67] found significant improvement not only in both pain (VAS) and functional scores (WOMAC) but also in MRI after intra-articular injections of ADMSC .In another study, Jo et al.[68]

evaluated the safety and efficacy of intra-articular injection of ADMSC in 18 patients with OA knee. The 6 month follow up results showed an improvement in pain and function (WOMAC) without causing adverse events, and reduced cartilage defects by regeneration of hyaline-like articular cartilage.

Conclusion

Orthobiologics is a vastly expanding field within musculoskeletal medicine, currently characterized by 4 generations: hyaluronic acid, platelet rich plasma, bone marrow

concentrate, and adipose derived mesenchymal stem cells. Future generations of Orthobiologics are currently being developed, most notably, amniotic tissue as an allogeneic source for mesenchymal stem cells. Although applications within each generation continue to expand, significant research and collaborative efforts are needed to increase our understanding of potential therapeutic benefits and further study the cellular constituents of each orthobiologic.

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