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Editorial Review Article

Understanding the Role of Platelet Rich Plasma, Bone Marrow Concentrate, Micro Fragmented Adipose Tissue, Stromal Vascular Fraction and Stem Cell in Osteoarthritis of the Knee: It's Time to Wake Up!

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Abstract

Osteoarthritis is a degenerative process resulting from decreased anabolic and increased catabolic activities in the articular cartilage and synovial membrane of joints. Osteoarthritis usually presents itself as pain, stiffness and joint deformity at a later stage. It is more common after the age of 50 years and is seen more in women than men [1]. Due to an increasing life span, the number of people having osteoarthritis (OA) of the knee is going to increase much fold during the next few decades. Conventional treatment of mild osteoarthritis of knee involves analgesic, lifestyle modification, weight reduction, joint support, and physiotherapy. Treatment options of advanced osteoarthritis with joint stiffness or deformity includes corrective osteotomy, partial or total knee replacement. Treatment options for moderate OA and non-responsive early knee OA are limited. Hyaluronic acid has been an important adjuvant in the treatment of mild to moderate OA over the last few decades [1,2]. It is believed to increase the endogenous production of hyaluronic acid [3], stimulate cartilage matrix synthesis and metabolism. It gives pain relief in osteoarthritis by inhibiting enzymes degrading cartilage and the inflammatory process [4]. But the effects of this treatment are short-lasting and need repeat injections at a 3-6 months interval [5].

Many types of blood-based and cell-based regenerative treatment methods have come up during the current decade. These regenerative products include Platelet Rich Plasma (PRP), Bone Marrow Concentrate (BMC), Mesenchymal Stem Cell (MSC), Microfragmented Adipose Tissue (MAT), Stromal Vascular Fraction (SVF) and Adipose-Derived Stem Cells (ADSC); they have generated a great interest and are offered with an unlimited potential of healing and regeneration in osteoarthritis of knee joint.

Keywords: *Platelet Rich Plasma; Bone Marrow; Adipose Tissue; Stromal Vascular Fraction; Stem Cell; Osteoarthritis*

Platelet rich plasma (PRP)

PRP is an autologous blood fraction with a platelet count above the baseline (1,50000 - 350000/µl,) or one million platelets/µl, or 3 - 5 times above the whole blood [6,7]. Platelet has alpha granules, which contain growth factors (PDGF, SDF1a, bFGF, EGF, IGF-1, TGB-1.), angiogenic factor (VEGF, FGF), homeostatic factors (Factor V, VWF) and fibrinogen [7-9]. When PRP is injected into the target site, platelets get activated after coming in contact with local collagen/tissue (best method of activation for sustained release of factors) and release the contents of alpha granules. PRP increases endogenous Hyaluronic acid and type II collagen production, improves chondrocyte prolifera-

tion, matrix production and cartilage remodeling [10,11]. It reduces interleukin-1 directed increased level of matrix metalloproteinase; helps in stem cell proliferation, differentiation, migration and homing [12]. It also acts a scaffold and tissue sealant [13] and has limited antimicrobial effects [13]. A standard PRP regimen consisting of 2 - 3 intra-articular injections of 4 - 6 ml of leucocyte poor PRP at 1 - 2 weekly interval provides a better result than HA during a period of 3 - 6 months, and which may continue up to one year [14-19]. PRP and HA may have a synergistic effect [21,22]; pain and swelling are the two most common complications with PRP, the incidence is more with leucocyte rich PRP and intra-osseous PRP treatment.

BJ Cole., *et al.* (2015) did a double-blind prospective randomized clinical trial involving 111 patients having osteoarthritis of the knee. Patients were divided into two charts; one received ultrasound-guided 3 weekly PRP injections while the others received 3 weekly hyaluronic acid injections. PRP group had statistically significant higher IKD knee score, higher IL6 in synovial aspirate and lower VAS score than Hyaluronic acid group at 6 months follow up. Lysholm and WOMAC score were better in the PRP group but were not statistically significant. Similarly, there was a significant difference in synovial concentration of catabolic markers in both groups (TNF-α, IL-1B/IL-F2, IL-1ra/IL-1F3, IL-6, and CXCL8/IL-8.). They concluded that pain and function improved significantly with both PRP and hyaluronic but PRP may be more effective in an active patient with osteoarthritis [22]. Sánchez M., *et al.* did a multicentric double-blind trial in 176 patients; patients were randomly divided and were given 3 weekly injections of PRP or hyaluronic acid. Mean age was 59.8 years; and M: F ratio was 48:52 [23]. At a 24 weeks PRP patients had 14.1% higher pain relief than hyaluronic acid injection but there was no statistically significant difference in WOMAC score in both groups. They also showed the similar results as by Brian., *et al.* that pain control is better in the PRP group but overall symptomatic relief and WOMAC score were found the same in both groups [23]. Filardo G., *et al.* conducted a randomized double-blind prospective trial and compared the efficacy of PRP and hyaluronic acid in 109 patients. Patients blindly received 3 weekly injections of hyaluronic acid or PRP [24]. The PRP group showed a higher rate of post-injection pain & swelling, both groups showed clinical improvement without any statistically significant difference. They concluded that results of PRP were similar to hyaluronic acid and it should not be given as a first-line treatment but results were slightly better in a lower grade of osteoarthritis [24]. They reported similar findings in another double-blind controlled trial; both treatments were effective in improving symptoms and functional score over time without any significant difference at different follow-up points or on the duration of effects [25].

Esteban Holguin conducted a prospective randomized controlled study in 150 patients having severe osteoarthritis of the knee. Patients received 3 weekly injections of hyaluronic acid or PRP [26]. The study showed a statistically significant better WOMAC score and visual pain scale in the PRP group at 3-6 months follow up. However, both groups showed a similar result in 12 months. They recommended PRP as a safe, effective and low-cost treatment of osteoarthritis in comparison to hyaluronic acid injection [26].

Bone marrow concentrate (BMAC)

It is prepared from the bone marrow aspirated from the iliac crest; posterior iliac crest harvest is richer in cellular content than from the anterior iliac crest. Small volume aspiration in 10 ml syringe yield more stem and progenitor cells than large [27] syringe aspiration (50 ml); single site aspiration has been shown to have similar quality of bone marrow as of multiple site aspiration [28].

It has easy and simple access, cells have more osteogenic and chondrogenic differentiation potential than adipose tissue-derived stem cell [29-31]; but percentage of stem cells [32] may be less (1 in 25000 to 1 in 100,000) than the adipose tissue but viability and quality is better in colony-forming unit than adipose origin of stem cells. Bone marrow aspiration content is centrifuged and concentrated to increase the total cells (more than 5 - 8 times), to reduce the number of red blood cells and plasma free hemoglobin. Bone marrow concentrate contains various growth factors like Beta Transforming growth factors (promote chondrocyte proliferation and differentiation); BMP-2 (chondrocyte proliferation, matrix synthesis, and hypertrophy); BMP-7 (promote extracellular matrix production); VGEF/ PDGF (angiogensis, tissue healing), FGF (chondrogenic differentiation), platelet & mesenchymal stem cell. FGF (chondrogenic differentiation). One initial single-blind placebo-controlled prospective randomized controlled trial involving BMAC and saline injection in osteoarthritic

knee showed that pain and function improved at six months in both the groups without any statistical difference [33]. Subsequently Brent Shaw [34] demonstrated that four injections of BMAC (13.80 days after the first treatment, 21.40 days after the second treatment, and 33.50 days after the third treatment) in osteoarthritic knee showed reduced resting pain (84.31%), active pain (61.95%), improved functional score (55.68%) and a mean 67% total overall improvement. One animal study showed BMAC addition to in Goettinger mini-pigs scaffold led to a significantly better healing of osteochondral defects [35] while another recent animal study [36] showed that BMAC significantly enhanced regeneration of the meniscus lesions in a rabbit in a time-dependent manner and in comparison to the PRP and control groups, where no healing could be observed. A single injection of BMAC followed by one PRP injection at one month showed reduced pain, better function, and quality of life in the osteoarthritic knee of 3 female patients [37]. Kenneth M., *et al.* [38] compared effects of BMAC (58 knees) with Microfragmented Fat (48 knees) and showed both reduced pain, improved the functional score and quality of life at 1.80 years without any significant difference between two groups.

Mesenchymal stem cells

Mesenchymal stem cells have been shown to act by paracrine and juxtracrine signaling [39,40] and to exhibit anti-inflammatory, anti-fibrotic (bFGF, AMD, HGF), angiogenic, mitogenic, anti-apoptotic [41,42] and immunoregulatory properties [PGE2, TSG-6, ECVs; 43-450]. They have been shown to have a low potential for overall homing [46-48] and low engraftment [49,50] or incorporation [49,50] in the target tissues or organ. These cells first facilitate to create a pro-growth environment by secretion of growth factors/cytokines/Extracellular Vesicles (EVs); which starts inhibiting the pro-inflammatory cytokines, anti-angiogenic factors, apoptotic and fibrotic factors. MSC produces TNFα-stimulated gene/protein 6 (TSG-6), prostaglandin E2 (PGE2) and indoleamine 2,3-dioxygenase (IDO); these promote the conversion of M1 macrophage (proinflammatory) to M2 macrophage (immunosuppressive) and reduce proliferation and cytotoxicity of Natural killer cells [45].

MSC also create Immuno-suppressive environment by secreting IL-10 and TGF-β [51,52], which inhibits lipopolysaccharide (LPS)-stimulated macrophages from secreting IL-1β and TNF-α [53]. MSCs have been shown to a have an immunosuppressive effect mediated mainly by inhibition of PGE2 leading to prevention of T cell proliferation when T cells are stimulated by the pro-inflammatory cytokine INF-γ, and express IL-6 and IL-10 to block macrophage differentiation towards dendritic cells [50]. MSC also inhibits the division of B cell during G0 and G1 phases [55,56]. Literature regarding the efficacy of MSC is conflicting and debatable. Lamo-Espinosa JM., *et al.* conducted [57] an A phase I/II multicenter randomized clinical trial involving injecting hyaluronic acid alone or in combination witth 10 or 100 millions cultured autologus cultured autologous BM-MSCs in 30 osteoarthritic knees. They concluded that single intraarticular injection of in vitro expanded autologous BM-MSCs together with HA is a safe and improves clinical and functional improvement of osteoarthritic knee.

Recent systemic review with metanalysis [58] and most of the other studies have shown that MSC therapy improves the VAS pain score, WOMAC score and functions compared to placebo or conventional treatment and it lasts up to 6- 12 months [59-65] and then it starts showing downward trend [60].

They have also been shown to have an insignificant improvement in cartilage quality. While one study reported improvement with both MSC and placebo up to 18 months and then the placebo group showed reduced response but MSC group continued to perform better than MSC [66].

Adipose-derived biological treatment

It has also easy access from the abdomen, buttock; again the number of MSC cells [67] in unit volume (2% of the entire cell population of lipoaspirate or 500 times more pluripotent cells than in equal amount bone marrow) is more than bone marrow. But quality, viability and osteogenic (same or superior one over the other) potential of bone marrow and adipose-derived stem cell-derived [68,69] is debatable.

Intra-articular knee injections of Adipose-derived stem cell (ADPSC) have been shown to reduce pain, improve function [70] which tend to persist for one year with low -medium dosage (1.0×10^7 - 5.0×10^7) and for two years with high dosages (1.0×10^8 AD [65,71]. Spasovski D., *et al.* [72] reported similar results with improvement in clinical symptoms and pain at 3 months with peak effects at 6 months. Michalek J., *et al.* [73] have shown that intra-articular injections of Stromal Vascular Fraction (SVF; 14.4 - 40.1 × 10^6 SVF cells) is a safe therapy for osteoarthritis of knee in 1856 joints in 1128 patients with grade 2 - 4 degenerative osteoarthritis ; improves clinical symptoms and high dosages (15×10^6 SVF cells) has long-lasting effects [74,75]. Microfragmented fat (MAT) is another adipose-derived biological product using mechanical processing (like Lipogem) of lipoaspirate without enzymatic digestion; intra-articular injections of MAT is safe and improving pain, function, and quality of life at 6 and 12 months [76].

Conclusions

PRP (Platelet Rich Plasma), BMAC (Bone Marrow Aspirate Concentrate), ADSC (Adipose-Derived Stem Cell), MSC (Mesenchymal Stem Cell), SVF (Stromal Vascular Fraction) and MAT (Microfragmented Adipose Tissue) are safe and effective treatment options for mild to moderate OA and in some cases of severe osteoarthritis of knee joints.

All of them have been shown to reduce pain, improve functions and quality of life for a variable period of 6 months to one year in majority of patients and up to two years in selected cases.

Literature regarding the radiological, histological or arthroscopic improvement in the cartilage remodeling, quality and cartilage volume is scanty.

PRP has been shown to have synergistic effects in combinations to other regenerative products.

Source of these regenerative products, retrieval methods, processing methods, nature of final products, administration (dosages, routes, site and interval of injection), the efficacy of one over the other are debatable and need more standardization and randomized studies with long term follow-up.

Better conducted double-blind randomized studies with long follow-up are required to understand and document the long- term safety and efficacy of this treatment.

Orthobiologic treatments are in the evolving phase and have unlimited potential to promote healing, repair, reconstruction, and regeneration. Regulatory authorities and the insurance company should accept them as a standard treatment to reduce the cost of treatment by avoiding major surgeries in some cases, reducing analgesics requirement and hospital admissions. They should work as a team with senior or expert regenerative physicians to provide training opportunities to young physicians and to recommend guidelines for indications of treatment, standardization of harvesting, processing, administration; and proper documentation of complications to improve the existing practices and prevent complications.

Its time to wake up; we as a responsible physicians, researchers and scientists should come together to project the clear picture and role of these regenerative products in different medical conditions so that all the involved parties (physician, patient, family member, insurance companies, regulatory authority) are confident about these treatments and value of these fantastic emerging healing opportunities are not spoiled by false claims of miraculous results and unwanted complications due to wrong choices of patients selection, commercial interests and due to inadequate training or experience in these regenerative procedures.

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