Bone Marrow Aspirate Concentrate for Orthopaedic Use

Jorge Chahla ▼ Jeremy A. Alland ▼ Nikhil N. Verma

Biological-based therapies are rapidly expanding for different musculoskeletal conditions because of their potential benefits including their minimal invasiveness, capacity for unprecedented healing, and potential for rapid recovery. In this regard, although several approaches have been reported in the literature, most of the body of the literature is increasingly based on platelet-rich plasma, bone marrow aspirate concentrate, and cell-based therapy studies. Although further basic science and clinical research is needed to elucidate the long-term outcome of these therapies in the treatment of several injuries, there is compelling evidence for their use for certain indications. The purpose of this article was to review the main aspects of bone marrow aspirate concentrate, which is one of the few forms of stem cell delivery approved by the Food and Drug Administration, and, furthermore, to critically assess the current evidence-based recommendations and identify potential avenues for development.

Stem cell treatments are widely pursued because of its potential for regeneration mainly driven by idealized outcomes that could not be translated in clinical practice thus far (Chahla et al, 2016a, 2016b; Dallo et al., 2017; Kraeutler, Chahla, LaPrade, & Pascual-Garrido, 2017). Stem cells are a group of cells from your own body that have the possibility to become any cell type depending on the signals that they receive. When you are conceived, you are composed of many stem cells that end up forming your organs and different tissues. This group of cells is more powerful when you are born, and therefore their healing potential is much sturdier. Throughout life, organs and tissues are constantly changing their cells and are replaced by new cells derived from your own stem cells. As you age, their potential and the number of stem cells diminishes, and therefore stem cells start to lose their potential to regenerate and aging signs become evident (Atesok et al., 2017).

Besides having a regenerative potential, stem cells are very powerful signaling cells, which mean that they can regulate the inflammatory response, and they can organize which proteins are needed in each case (Whitney et al., 2017). Because of this, stem cells have been proposed as a potential regenerative source for patients with osteoarthritis (OA). Research efforts are focused on determining the ideal source of stem cells (they can be extracted from blood, bone marrow, fat, muscle, and virtually every tissue in the body).

Here, it is very important to differentiate between a single aspiration or harvesting of the cells, which can be further concentrated (Chahla et al., 2017), versus true stem cell therapy when these cells are isolated, tested for their regenerative capacity, cultured for a couple of weeks, and then reimplanted. For the first category, this is a same-day procedure where the cells are extracted, concentrated, and then reimplanted. The most well-known procedure is called bone marrow aspirate concentrate. This is Food and Drug Administration (FDA) approved because it requires minimal manipulation of the harvested cells (no chemical addition). However, the number of cells present within the aspiration, and a type of cells present, is not optimal, as it has been found that for example in bone marrow aspirates the amount of cells present is 0.001% (Chahla et al., 2016c). Also, the regenerative potential of the cells may not be optimal because this is a mixture of stem cells with great, medium, and poor regenerative potential.

The second procedure is not FDA approved, and therefore it cannot be performed in the United States if it is not within the limits of a clinical trial (offered in other countries or islands to avoid the regulatory burden). It involves harvesting and isolating the stem cells with the greatest potential to grow and multiplying them by sequential culturing processes that will produce millions of stem cells with the greatest regenerative potential. All of these potential benefits have been proven mostly in vitro, although results and their safety profile have not been completely established in humans and that is the reason why they are not yet approved by the FDA as of

Jorge Chahla, MD, PhD, Midwest Orthopaedics at Rush, Chicago, IL.

Jeremy A. Alland, MD, Midwest Orthopaedics at Rush, Chicago, IL.

Nikhil N. Verma, MD, Midwest Orthopaedics at Rush, Chicago, IL.

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now. The cells are similar to the cells present in cancer (which can grow without stopping), and therefore have the capacity to become any tissue. If they have the appropriate signaling, they can become the desired tissue, but if they do not have the right signal, they can create another tissue as demonstrated by animal studies, where for example bone was created instead of forming cartilage in cartilage defects. Another important point to consider is that, once the desired tissue has been made, the cells should stop regenerating, because if they keep promoting regeneration and proliferation and multiplying without a stop sign, they can create a tumor.

Another critical point is the mode of delivery of stem cells, which remains a challenge. As of now there are two main ways of implanting stem cells (Chahla & Mandelbaum, 2018). The first mode is to deliver the stem cells as an injection with a fluid in which the cells are contained (when there is no specific injury, but it is rather a disseminated injury like OA), and the second is the delivery of the cells through a scaffold that can be implanted. The potential benefit of using a scaffold is that the cells are going to remain in the place that we want them to be. However, recent research has reported that the stem cells that actually induce healing may not be the same cells that we inject and that they might be coming from different parts of the body (the injected stem cells act as signaling cells calling other cells in your body to repair the tissues). Also, as these cell actions depend on signaling (they need somebody to tell them where they are and how to behave), when they are encapsulated in a scaffold they might not be able to listen or see those signals and therefore not function in the way that we expect (creating bone instead of cartilage for example). Bone marrow aspirate has a potential to diminish inflammation even further (when compared with platelet-rich plasma) because of the presence of interleukin-1 receptor antagonist, which is a powerful blocker of inflammation within the joint, which could explain the relative speedy action after the bone marrow injection.

Despite popular belief and advertisements, the information available about stem cell outcomes in human patients is very limited (there is less information than there is for platelet-rich plasma injections) (Chahla et al., 2016a, 2016c; Kraeutler et al., 2017; Piuzzi et al., 2017a, 2017b). There are few randomized clinical trials looking at the effectiveness of bone marrow aspirate for the treatment of OA. The overall reported outcomes are decent with a relatively safe profile (no major adverse events reported). Recently, researchers from the Mayo Clinic reported on 25 patients who had bilateral knee OA. They injected bone marrow aspirate concentrate in one knee and saline (only fluid with salt) in the other knee. They reported no difference at 6 months or 1 year between the groups. Outcomes for strict stem cell therapies (culture expanded) are also limited. A recent review identified only six trials (for OA and cartilage defects) that reported that only modest improvement was found and that a placebo effect could not be ruled out with stem cell injections!

The reported frequency of adverse effects after the procedure occurs in 6%–10% of the patients. Self-limited pain and swelling are the most commonly reported adverse events. For culture expanded cells, as stated before, it is worrisome that these cells can further develop into unwanted tumoral cells, which is still a concern. Furthermore, manipulation in the laboratory has risks of contamination of the cells. Researchers from Stanford and Colorado State University stated that unwanted tissues formed after the repair of a cartilage injury in a horse model (bone instead of cartilage) (Goodrich et al., 2016).

In conclusion, despite the increasing and widespread use of biological treatment agents, there are still several areas that need further study and clarification. No consensus exists on the algorithm for treatment, indications, optimal protocol of processing, and delivery and outcome reporting. Although essential advancements have been made in the field of biologics, these therapies are still in their beginnings. In order to advance the knowledge, it is important to first define a minimal standard for each of these treatments. However, there is decent evidence that supports the use of biological approaches with better results for the symptomatic treatment of knee OA when compared with other several therapies (such as steroids, ozone, and hyaluronic acid). Although cell-based treatments have shown promising results, further understanding of the joint cytokine milieu at the time of administration and cell epigenetic and genetic signaling will drive a significant improvement that could generalize its use. It is the authors' opinion that the current best practice for these treatments in patients with OA occurs when standard treatments such as corticosteroid injections, viscosupplementation injections, and physical therapy have not yielded satisfactory outcomes in controlling the symptoms for a reasonable time. It is imperative that the clinician be direct and transparent about the expectations of the biologic treatments, discounting the potential for regeneration, discussing costs, and emphasizing the clinical benefits. Finally, it is strongly encouraged that clinicians, at minimum, participate in a registry with patient-reported outcomes to add to the existing data regarding these treatments.

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