

Letter to the Editor: Stem Cells Combined With Platelet-rich Plasma Effectively Treat Corticosteroid-induced Osteonecrosis of the Hip: A Prospective Study

Nicolas S. PiuZZi MD

To the Editor,

I read the study by Houdek and colleagues [8] with great interest and believe that the orthopaedic community at large will benefit from developing

(RE: Houdek MT, Wyles CC, Collins MS, Howe BM, Terzic A, Behfar A, Sierra RJ. Stem Cells Combined With Platelet-rich Plasma Effectively Treat Corticosteroid-induced Osteonecrosis of the Hip: A Prospective Study. *Clin Orthop Relat Res*. 2018; 476:388–397).

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N. S. PiuZZi, Orthopaedic Regenerative Medicine and Cellular Therapies Clinical Scholar, Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, OH, USA, and Instituto Universitario del Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Nicolas S. PiuZZi MD (✉), Department of Orthopaedic Surgery, Cleveland Clinic, 9500 Euclid Ave., Cleveland, Ohio 44195 USA, Email: piuzzin@ccf.org

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and implementing cell-based therapies for patients with osteonecrosis of the femoral head (ONFH) [4]. Still, there are gaps in our knowledge that remain.

Along with the need for randomized controlled trials that compare the efficacy of cell-based therapies to core decompression or nonoperative treatment alone, two additional issues need to be addressed: (1) Nomenclature and (2) heterogeneous and deficient reporting.

Nomenclature

Across different areas, authors have noted the importance of solving nomenclature ambiguities, and have called on journals to implement tools to ensure the proper authentication of materials [6, 13, 14]. We should standardize the nomenclature in cellular therapies.

More than 30 years ago, a breakthrough occurred after the discovery that fibroblastic colonies, derived from a single colony forming unit–fibroblastic (CFU-F), formed when bone marrow cells were cultured in vitro [10]. Building on this observation, mesenchymal stem cells (MSCs), the plastic-adherent cells isolated from bone marrow and other sources that can be culture expanded

and differentiated to different lineages, were promoted and widely tested for multiple applications [2]. In contrast, the biologic properties of an unfractionated population of cells obtained from different tissues (such as nucleated cells from bone marrow or fat) do not meet the generally accepted criteria for adult stem cell activity. “Stem cells” should have at least two characteristics: (1) The ability to proliferate and (2) the ability to develop into mature cell types that have distinctive morphologies and specialized roles. Generally, stem cells produce progenitor cells, which are partly differentiated cells that divide and give rise to differentiated cells [1, 3]. As a result, rendering the name “MSC” to all nucleated cells is scientifically inaccurate and potentially misleading [7].

To address this inconsistency, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) proposed criteria to define human mesenchymal stromal/stem cells: “First, MSC must be plastic-adherent when maintained in standard culture conditions. Second, MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules. Third, MSC must differentiate to osteoblasts, adipocytes and chondroblasts in vitro. While these criteria

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will probably require modification as new knowledge unfolds, we believe this minimal set of standard criteria will foster a more uniform characterization of MSC and facilitate the exchange of data among investigators” [5]. Therefore, if bone marrow is processed by density separation (centrifugation) to concentrate the total nucleated cells, a more-appropriate nomenclature would be: Bone marrow nucleated cells (BMNC). It is true that of all BMNC, a small fraction can be plastic-adherent and show CFU capability (approximately 1 CFU per 4000 nucleated cells to 1 CFU per 20,000 nucleated cells [1, 2]); however, this is not true for the vast majority of BMNC.

Heterogeneous and deficient reporting

Biological therapies, including cellular therapies, can potentially restore local cell populations or modulate inflammation, but without standardized quantitative and qualitative characterization, it will be challenging to determine the efficacy of these therapies. For example, cellular therapies for the treatment of ONFH have low complication rates with no major adverse event reported. Cellular therapies could potentially improve patient-reported outcome measures (PROMs) with a lower likelihood of developing more-advanced stages of ONFH [12]. However, current studies are limited by small sample sizes and vary widely with respect to the cellular therapies delivered, including variation in cell sourcing, cell harvest, cell processing, cell characterization, cell delivery, adjuvant therapies, and assessment of outcomes [11].

To overcome this limitation, it is important to standardize the reporting of

both the preparation and composition of bone marrow concentrates (BMC) and platelet-rich plasma (PRP) [3]. By doing this, the compositional assessment of BMC and/or PRP (with respect to such factors as platelet count, red blood cells, nucleated cells, and volume) can be later correlated to validated outcome assessment tools for assessing symptoms modifying effects (eg, PROMs) or disease modifying effects (eg, MRI). Furthermore, when performing CFU assays to assess the population of stem and progenitor cells present in native tissues (known as connective tissue progenitors [9]), researchers should attempt to implement objective assessment tools as standardized by American Society for Testing and Materials International [1]. Additionally, further studies should evaluate and characterize other stem- and progenitor-cell populations including hematopoietic and endothelial stem cells, which could potentially be relevant as well.

Overall, the development and implementation of cellular therapies with potential disease-modifying effects remains a challenge in our field. Therefore, their effective clinical assessment and improvement will demand: (1) High-quality methodology in study design (blinded, randomized clinical trials), (2) special attention to standardized nomenclature and quantitative methods for cell harvesting, processing, characterization, and delivery, and (3) standardized reporting of clinical and structural outcomes.

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