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Extended Abstract

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Assessing clinical implications and perspectives of the pathophysiological effects of erythrocytes and plasma free hemoglobin in autologous biologics for use in musculoskeletal regenerative medicine therapies

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Autologous biologics, defined as platelet-rich plasma (PRP) and bone marrow aspirate stem cell concentrate (BMSC), are cell-based therapy treatment options in regenerative medicine practices, and have been increasingly used in orthopedics, sports medicine, and spinal disorders. These biological products are produced at point-of-care; thereby, avoiding expensive and cumbersome culturing and expansion techniques. Numerous commercial PRP and BMSC systems are available but reports and knowledge of bio-cellular formulations produced by these systems are limited. This limited information hinders evaluating clinical and research outcomes and thus making conclusions about their biological effectiveness. Some of their important cellular and protein properties have not been characterized, which is critical for understanding the mechanisms of actions involved in tissue regenerative processes. The presence and role of red blood cells (RBCs) in any biologic has not been addressed extensively. Furthermore, some of the pathophysiological effects and phenomena related to RBCs have not been studied. A lack of a complete understanding of all of the biological components and their functional consequences hampers the development of clinical standards for any biological preparation. This lecture aims to review the clinical implications and pathophysiological effects of RBCs in PRP and BMSC; emphasizes hemolysis, eryptosis, and the release of macrophage inhibitory factor; and explains several effects on the microenvironment, such as inflammation, oxidative stress, vasoconstriction, and impaired cell metabolism. Autologous biologics, defined as platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMC), are cell-based therapy treatment options in regenerative medicine practices, and have been increasingly used in orthopedics, sports medicine, and spinal disorders. These biological products are produced at point-of-care; thereby, avoiding expensive and cumbersome culturing and expansion techniques. Numerous commercial PRP and BMC systems are available but reports and knowledge of bio-cellular formulations produced by these systems are limited. This limited information hinders evaluating clinical and research outcomes and thus making conclusions about their biological effectiveness. Some of their important cellular and protein properties have not been characterized, which is critical for understanding the mechanisms of actions involved in tissue regenerative processes. The presence and role of red blood cells (RBCs) in any biologic has not been addressed extensively. Furthermore, some of the pathophysiological effects and phenomena related to RBCs have not been studied. A lack of a complete understanding of all of the biological components and their functional consequences hampers the development of clinical standards for any biological preparation. This paper aims to review the clinical implications and pathophysiological effects of RBCs in PRP and BMC; emphasizes hemolysis, eryptosis, and the release of macrophage inhibitory factor; and explains several effects on the microenvironment, such as inflammation, oxidative stress, vasoconstriction, and impaired cell metabolism. Regenerative medicine methods, in particular orthobiologic injections, offer solutions to a number of compelling clinical problems such as tendinopathies and degenerative arthritis which have previously had limited response to medications, rehabilitation, surgery, or joint replacement surgery. Recently, biological therapies have emerged as promising treatment options for many musculoskeletal disorders affecting young adults and the elderly. Autologous biologics prepared at point-of-care, such as platelet-rich plasma (PRP) and bone marrow concentrate (BMC), have become important autologous biological therapeutics in health care strategies for enhanced tissue repair, regenerative processes, and immunomodulation. Within orthobiology, biological therapies utilizing autologous PRP and BMC frequently include the following clinical problem: osteoarthritis (OA), tendon repair, focal chondral lesions, and soft tissue (meniscus, ligaments) repair. In addition, there is early promise in the treatment of nerve conditions and injury. PRP therapies and several related treatment protocols have evolved immensely over the past 20 years. Through laboratory, experimental, and clinical research, followed by meta-analyses, physicians, medical practitioners, and scientists have gained a better understanding of how PRP affects cellular physiology. Notably, they have gained further insight into the functions of some specific biological components in the platelet proteome that affect PRP-treatment outcomes when used to treat various musculoskeletal pathologies. The biological rationale for the clinical use of PRP includes the local delivery of the intra cellular platelet vesicles containing growth factors, cytokines, lysosomes and chemokines. Furthermore, PRP has been recognized to modify inflammatory responses and to stimulate cell proliferation and cell differentiation. The rationale for BMC applications is the abundant and varied bone marrow cell content, such as bone marrow-mesenchymal cells (BM-MSCs), hematopoietic-progenitor cells, platelets, white blood cells, and erythrocytes that are readily accessible and largely dispensable. BM-MSCs are relatively easy to acquire by bone marrow aspiration (BMA) from a variety of anatomic sites with minimal morbidity. An effective BM-MSC injection depends on the quality of the initial BMA procedure, which should minimize trauma to the cellular content of the bone marrow niche while maximizing cellular yields and simultaneously avoiding peripheral blood infiltration.

Moreover, the authors believe that a BMA sample should always be followed by a 2-step centrifugation procedure to concentrate the essential cellular content of BMC above the baseline counts, according to the recommendation of Pittenger BM-MSCs have been found to differentiate into mesodermal lineage cells, such as osteoblasts, endothelial cells, adipose tissue, smooth muscle cells, and multiple musculoskeletal tissue types, including chondrocytes, and tenocytes. These bio-cellular capabilities have led to the use of BM-MSCs as a potential strategy for treating various diseases because they promote biological processes, such as angiogenesis, cell proliferation, and differentiation. Furthermore, the cellular component of BMC can synthesize mediators (cytokines and trophic factors) that participate in tissue repair processes, immune modulation, and the regulation of inflammatory processes. Similar to PRP, viable, autologous prepared BM-MSCs are used to treat a variety of musculoskeletal disorders, such as chondral defects, osteoarthritis, and rotator cuff lesions. However, the discrete characterization of PRP and BMC biological therapies are still in their infancy relative to surgical interventions and pharmaceuticals. One reason for this immaturity may be the lack of standardization of PRP and BMC final product characterization, the number of the cellular components within the final product delivered to a specific patient. This lack of regulatory standards for clinical practice and the limited consensus on specific formulation characteristics of PRP and BMC products likely contribute to inconsistent patient outcomes, as reported in the literature. RBCs can be damaged as a result of several immune-mediated processes and high shear forces during blood collection for PRP preparation and bone marrow aspiration, or inadequate centrifugation and concentration protocols. As a consequence, the RBC cell membrane will start to disintegrate and hemolysis, with the release of plasma free hemoglobin (PFH) will occur and is characterized by the release of hemoglobin (Hb) and hemin and iron from lysed RBCs. The disintegration of RBC's lead to the development and release of toxic Hb forms, capable of inducing oxidative stress and pro-inflammatory PFH reactions in plasma and tissues. These pathophysiological conditions have the potential of inducing RBC suicidal cell death, eryptosis. During eryptosis, platelet activating factor (PAF) is released from RBCs, exposing phosphatidylserine to the cell surface, affecting in particular RBC-endothelial interaction. This phenomenon is known to contribute to vascular damage or microcirculatory blood flow irregularities. Another significant consequence of PFH is the release of macrophage migration inhibitory factor (MIF), since RBCs contain large concentrations of this enzymatically and chemotactically active cytokine. MIF is identified as a very potent inflammatory cytokine.

Bottom Note: *This work is partly presented at* 6th World Congress on NATURAL PRODUCT & SYNTHETIC CHEMISTRY June 24-25, 2019 | New York, USA.