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THE ROLE OF *PLATELET RICH PLASMA* IN GENU OSTEOARTRITIS PAIN

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ABSTRACT

Osteoarthritis is a joint disorder that happen most often worldwide. Pain and loss of function is main clinical sign in genu osteoarthritis that could come from periosteal nerve stretches, intraosseal hypertension, joint capsule stretches, intra-articular hypertension, ligament stretches, subchondral bone micro fracture, bursitis, and muscle spasm. Current therapy approach focuses on preventing progressivity and reducing symptoms by developing a non-invasive procedure. Non-operative therapeutic intervention that involves intra-articular injection in knee joints plays an important role in genu osteoarthritis management.

Platelet rich plasma (PRP) is a plasma fraction that contains many platelets, has an autologue growth factor and high concentrated protein secretion that could improve cellular, tendon, ligament, muscle, and bone level healing process. Growth factor contained by PRP is responsible for anti-inflammatory effect through inhibitory effect in Nuclear factor-kB (NFkB) cascade, thus inhibit inflammatory mediator production along with decrease of COX2 expression.

Roles of PRP towards NFkB deactivation could decrease chondrocyte inflammation, restore anabolic activity, and inhibit monocyte migration that could prevent osteoarthritis progressivisity and reduce pain. PRP pathophysiology mechanism in healing process has made PRP an option for pain management in genu osteoarthritis.

Keywords : Osteoarthritis genu, platelet rich plasma, Nuclear factor-κB (NFkB), Human & Medicine
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INTRODUCTION

Osteoarthritis (OA) is the most prevalent disorder of joint with knee and hip OA prevalences around the world are 3.8% and 0.85%.[1] Pain is still being global problem and its current pain treatment is still dissatisfying due to its chronicity and existing drugs' side effects.[2] Pain and functional loss are main clinical features of knee osteoarthritis and usually complained by patients when seeking for clinician's treatment.[3] The pain ethiology in osteoarthritis are multifactorial. They can be periosteal nerve fiber stretch, intra-osseous hypertension, joint capsule stretch, intra-articular hypertension, ligament strain, subchondral bone microfracture, bursitis, and muscle spasm[4].

Most of the treatment for osteoarthritis has not shown satisfactory results. Conservative management has good results for initial management, but the role of conservative therapy is still limited in modifying the occurring structural abnormalities.[1] There is no pharmacological agent that can stop the progression of OA. Available approaches concentrate on progression prevention and symptoms reducement by expanding non-invasive procedures. Non-surgical therapeutic interventions including intra-articular injection of knee joint which have an important role in the management of genu OA[5].

Recently, the injection of platelet rich plasma (PRP), which is one of biologic therapy, has become an attractive treatment option for relieving pain and improving function in OA patients[6]. PRP therapy broadly defined as plasma fraction with lot of platelets which has autologous growth factors and secreted high concentrations of proteins that can improve the healing process of cellular, ligament, tendon, bone,

and muscle level.[7] Various pathophysiological mechanisms of PRP for healing process have made PRP as an option for pain management in genu OA.[7] Several studies have shown that using PRP as the OA treatment is more preferable than hyaluronic acid as there is an increament in the total score of Western Ontario & McMaster Universities (WOMAC) and other parameters.[8]

GENU OSTEOARTHRITIS

Osteoarthritis is a degenerative and inflamed of joint with pathological structural changes.[9] Based on the American College of Rheumatology (ACR), OA is joint pain occured between days and months, with crepitus in joint motion and morning stiffness. According to WHO, the definition of genu OA is a combination between ACR definition and appropriate radiological results.[10] The radiological definition for OA is the formation of osteophytes, joint fissures, subchondral sclerosis, and subchondral cyst formation.

The pathogenesis of genu OA is related to biomechanical and phytochemical changes in the cartilage of the knee joint. Cartilage keeps the bone surfaces move painlessly and keeps their friction low.[11] The thickness and quality of cartilage will be decreased, thinner, and softer so that it becomes easy to crack and crumble in OA. Bone can grow and the osteophyte formation occurs.[12] Inflammatory processes and vascular pathology, combined with cell death, meniscal changes, bone remodeling, and subchondral sclerosis, result a vicious cycle of OA progression that can be aggravated by exaggerated mechanical pressure and oxidative harm.[13]

Synovial inflammation begins when synovial cells ingest damaged products through phagocytosis and produces proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and metalloproteinases. This condition gives a reverse manifestation for cartilage and directly affects the cartilage destruction.[14]

Pain mechanism in genu OA is preceded by the fibrinogenic activity increased and fibrinolytic activity decreased in cartilage of OA patients.[15] This process causes a thrombus and lipid complex in the subchondral blood vessels which causes subchondral tissue ischemia and necrosis and results the emergence of chemical mediators such as prostaglandins and interleukins. Then it continues as bone angina through the subchondral which is known to be sensitive nerve endings that transmit pain.

Pain also results from the release of chemical mediators such as kinins and prostaglandins that cause joint, tendon, or ligament stretching and extra-articular muscle spasm due to overwork. Joint pain is also caused by the pressing of osteophytes on the periosteum and spinal cord nerve roots and the increament of intramedullary venous pressure due to intramedullary venous stasis from the remodelling process in trabeculae and subchondral.

Histochemical studies show that there are many type IVa nerve endings found on joint capsules, tendons, retinaculum, fat pads, synovium, subchondral bone and surrounding ligaments. These nerve endings find pressure and mediate proprioception throughout joint motion. Muscle and fascia also have many nerve

endings that are sensitive to substance P, mediate nociceptors and several mechanoreceptors.[16]

PLATELET RICH PLASMA (PRP)

PRP is a biological product which is known as part of the autologous blood plasma fraction with platelet concentration above the average. PRP was defined as the concentration of 1,000,000 platelets/L in 5 ml plasma volume.[17] PRP does not contains high levels only but also complement of clotting factors remaining at normal physiological levels. PRP is enriched by various Growth Factors (GF), chemokines, cytokines, and other plasma proteins.[18]

PRP is gained from blood samples taken from patients at the time of treatment. Taking 30 cc of venous blood will generate 3 – 5 cc of PRP. The formulation of PRP begins with the adjunct of citrate to the blood in order to bond calcium ions and prevent the cascade of clotting. Then one or two steps of centrifugation are carried out. In the initial phase of centrifugation, plasma and platelets are separated from erythrocytes and leukocytes. Erythrocytes (7 meters in diameter) and leukocytes (7-15 meters) are much larger than platelets, which are 2 meters in diameter. The second centrifugation step concentrates the platelets, thereby generating PRP which is separated from the plasma containing small amount of platelets. PRP also contains white blood cells and several proteins which neutrophils and monocytes can trigger local inflammatory effects and facilitate the tissue healing.[19]

Biologically, PRP has wide-dimensional wound healing effects. This mechanism occurs because of the growth factors and cytokines possessed by PRP which able to accelerate the healing process.[20] The possible consequence of PRP is closely associated to the molecular effects contained in platelet -granules. Bioactive molecules contain growth factors and cytokines, including transforming growth factor-β (TGF-β), insulin-like growth factor (IGF-I, IGF-II), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF)), epidermal growth factor (EGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and endothelial cell growth factor. Bioactive molecules have a main role in accelerating the healing process because they regulate angiogenesis, reorganize the extracellular matrix, influence the recruitment, proliferation, and differentiation of stem cells.[21]

PRP IN GENU OSTEARTRITIS

The PRP anti-inflammatory effects on chondrocytes is the outcome of nuclear factor-B transactivation inhibition mediated by hepatocyte growth factor (HGF) using specific inhibitors.[22] NFkB has been considered as a target for therapeutic intervention in OA. Cyclooxygenase-2 (COX2), which is known to trigger the synthesis of prostaglandin (PG) E2 from arachidonic acid and pain, is also mediated by NFkB.[23] PRP can trigger the synoviocytes to produce Hepatocyte Growth Factor (HGF), Platelet Derivative Growth Factor (HGF), Platelet Derivative Growth Factor (HGF), PDGF), and Insulin like Growth Factor (IGF) which can inhibit the NFkB signaling cascade.[24]

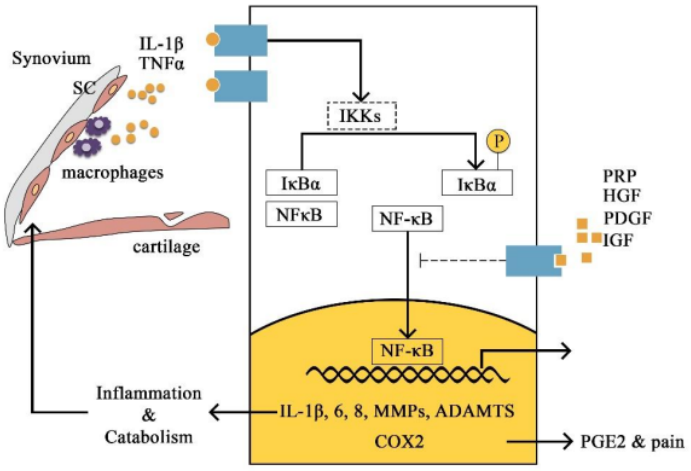

Figure 1. PRP Mechanism on Genu OA PAin[24]

Cartilage degeneration with the appearance of Vascular Endothelial Growth Factor (VEGF) receptors and high VEGF can lead to skeletal and osteophyte formation. High concentrations of VEGF in synovial fluid reflect the increament of vascular turnover and local synthesis.[25] The mechanism of PRP in angiogenesis through the balance of VEGF and HGF secretion can optimize the analgesic and anti-inflammatory effect in OA.[26]

PRP also contributes to cartilage repair in OA. Cartilage regenerated with PRP exhibited stronger mechanical properties against stress associated with an increase in the thickness of the engineered cartilage and an increase in the content of glycosaminoglycans.[27]

OA progression can be inhibited by maintaining joint homeostasis and repairing the joint microenvironment. PRP injection can directly alter synovial fluid changes or indirectly affect the local joint environment throughout chondrocytes and synoviocytes.

PRP can also result in the secretion of lubricin from chondrocytes along with cell proliferation and synthesis of hyaluronate. The combination of lubricin and hyaluronic acid can contribute to reduce distress and eliminate shear forces in synovial fluid.[28]

PRP injection in genu OA aims to build cartilage repair, reduce OA symptoms, and delay joint surgery.[29] PRP injection has been shown to affect the whole environment especially in short-term improvement and is considered as secure procedure with more favorable results compared to other alternative treatments.[5]

PRP interventions vary from 1 injection, 2 injections in a month, 3 injections in 15 day intervals, or 21 day intervals with a dose of 3-6 ml, but mostly applied are 3 PRP injections at 1 week intervals.[30]

The autologous and non-toxic nature of PRP is one of positive points by using PRP as genu OA treatment. Based on the pathophysiology and mechanism of PRP, clinically PRP is widely used to treat acute and chronic injuries or trauma. The results obtained are the high rate of wound healing and significant reduction in pain scale which can improve patient's quality of life.[5,7]

CONCLUSION

The role of Platelets Rich plasma (PRP) in the improvement of genu OA pain through the biological response changes of the Nuclear Factor Kappa B (NFkB) pathway. The growth factors present in PRP as HGF, IGF-1, and PDGF are responsible for the anti-inflammatory effect through their inhibitory effect on the

NFkB cascade. They inhibit the production of inflammatory mediators along with a decrease in COX2 expression. The role of PRP in NFB deactivation are to lower chondrocyte inflammation, restore anabolic activity, and inhibit monocyte migration in order to prevent OA progression and reduce pain.

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DECLARATION OF INTEREST

The Authors declare that there is no conflict of interest

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