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NARRATIVE REVIEW **PAIN MANAGEMENT**

The role of platelet rich plasma in knee joint pain

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Abstract

Osteoarthritis (OA) is a joint disorder is common worldwide. Pain and loss of function are the main clinical sign in knee joint OA 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 progression and reducing symptoms by using a non-invasive procedure. Non-operative therapeutic intervention, that involves intra-articular injection in the knee joints, plays an important role in OA management.

Platelet rich plasma (PRP) is a plasma fraction that contains concentrated platelets, has an autologue growth factor and high concentration of proteins that could improve healing process at cellular, tendon, ligament, muscle, as well as bone related tissue injury. Growth factor contained in PRP is responsible for anti-inflammatory effect through its inhibitory effect on Nuclear factor-kB (NFkB) cascade, thus it inhibits the inflammatory mediator production along with decreased COX2 expression.

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

Abbreviations: OA- Osteoarthritis; PRP - Platelet rich plasma; NFkB - Nuclear factor-kB; COX2 - Cyclooxygenase-2; HGF – Hepatocyte growth factor; TGF-β - Transforming growth factor-β; IGF - Insulin-like growth factor; PDGF - Platelet-derived growth factor; FGF - Fibroblast growth factor; EGF - Epidermal growth factor; VEGF - Vascular endothelial growth factor

Key words: Osteoarthritis knee joint; Platelet rich plasma; Nuclear factor-κB (NFkB); Human; Medicine

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1. Introduction

Osteoarthritis (OA) is the most prevalent disorder of the body joints, with knee and hip joint OA prevalence around the world being 3.8% and 0.85% respectively.[1] Pain is still remains a serious global problem and the current pain treatment modalities are still regarded as unsatisfactory due to its chronicity and high drug side effects.[2] Pain and functional loss are main clinical features of the knee OA, complained by patients when

seeking for clinician's help.[3] The factors associated with pathogenesis of OA 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 etc. [4]

Most of the common treatment for OA have not been proved satisfactory. 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 amelioration by expanding non-invasive procedures. Non-surgical therapeutic interventions include intra-articular injection of knee joint which have an important role in the management of knee joint OA. [5]

Recently, the injections of platelet rich plasma (PRP), which is one of the biological therapies, have become an attractive treatment option for relieving pain and improving function in OA patients. [6] PRP therapy is broadly defined as plasma fraction with lot of platelets which have autologous growth factors and high concentrations of proteins that can improve the healing process within damaged cells, ligaments, tendons, bone, and muscles.[7] Various pathophysiological mechanisms involved in PRP therapy for healing process have made PRP a prefered option for pain management in knee joint OA. [7] Several studies have shown that using PRP for the OA treatment is preferable than hyaluronic acid as there is an increament in the total score of Western Ontario & McMaster Universities (WOMAC) index and other parameters. [8]

2. Knee Joint OA

OA is a degenerative inflammation of the joint with pathological structural changes. [9] According to the American College of Rheumatology (ACR), OA is joint pain occuring in days to months, with crepitus on joint motion and morning stiffness. The WHO definition of knee joint 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 knee joint 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 making it thinner and softer, so that it becomes easy to crack and crumble in OA. Bone can grow abnormally leading to osteophyte formation.[12] Inflammatory processes and vascular pathology, combined with cell death, meniscal changes, bone remodeling, and subchondral sclerosis, start 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 produce proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and metalloproteinases. This condition produces an adverse manifestation for the joint cartilage and directly results into the cartilage destruction.[14]

Pain mechanism in knee joint OA is preceded by the increased fibrinogenic activity and decreased fibrinolytic activity in the 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 into induction of chemical mediators such as prostaglandins and interleukins. Then it continues as bone angina through the subchondral part which is known to harbor the 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. Compression by the osteophytes on the periosteum and the exiting spinal nerve roots and the increased intramedullary venous pressure due to venous stasis from the remodelling process in trabeculae and subchondral, also contribute to the genesis of pain.

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 sense pressure and mediate proprioception throughout the joint motion. Muscle and fascia also have many nerve endings that are sensitive to substance P, mediate nociceptors and several mechanoreceptors.[16]

3. 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 contain high concentration of platelets 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 produced from venous blood samples taken from the patient at the time of treatment. Taking 30 ml of venous blood will generate 3–5 ml of PRP. The formulation of PRP begins with the addition of citrate to

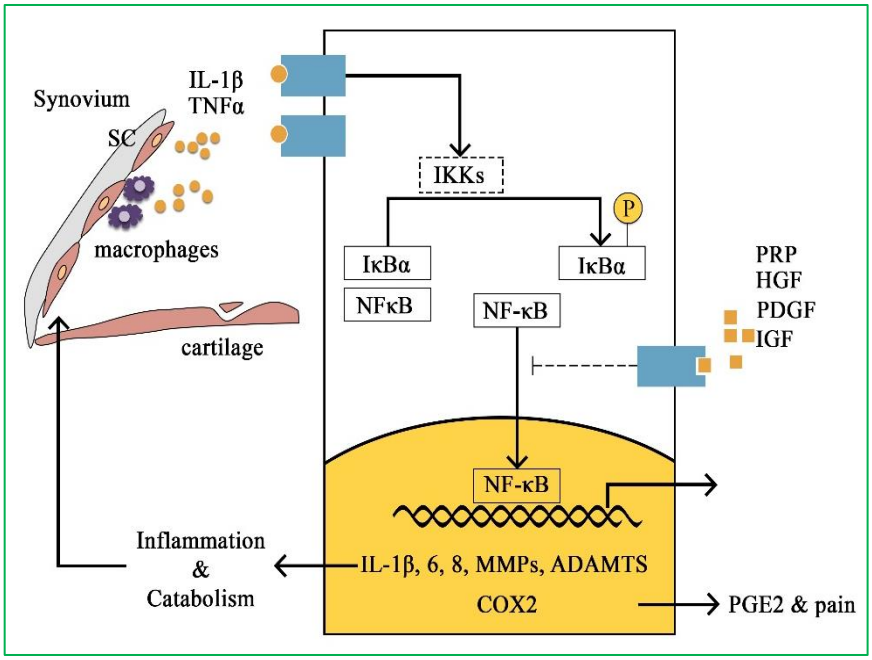

Figure 1: PRP mediated effect on knee joint OA pain24

the blood in order to bond calcium ions and prevent the cascade of clotting. Then one or two cycles of centrifugation are carried out. In the initial phase of centrifugation, plasma and platelets are separated from the erythrocytes and leukocytes. Erythrocytes (7.8 µm in diameter) and leukocytes (14-16 µm) are much larger than platelets, which are just 2 µm in diameter. The second centrifugation cycle 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 in the neutrophils and monocytes, which can trigger local inflammatory effects and facilitate the tissue healing.[19]

Biologically, PRP has wide-ranging wound healing effects. This occurs because of the growth factors and cytokines possessed by PRP and are capable to accelerate the healing process.[20] The possible consequence of PRP injection 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 the stem cells.[21]

4. PRP in Knee Joint OA

The PRP mediated anti-inflammatory effects on chondrocytes is the outcome of nuclear factor-B transactivation inhibition mediated by 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 the arachidonic acid and pain, is also mediated by NFkB.[23] PRP can trigger the synoviocytes to produce HGF, PDGF, and IGF, which can inhibit the NFkB signaling cascade.[24]

Cartilage degeneration starts with the appearance of VEGF receptors and high VEGF can lead to skeletal and osteophyte formation. High concentrations of VEGF in synovial fluid reflects the rapid vascular turnover and localized synthesis.[25] The mechanism of PRP in angiogenesis through the balance of VEGF and HGF secretion can optimize the analgesic and anti-inflammatory effects in OA.[26]

PRP also contributes to the 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. Lubricin is a chondrocyte-secreted glycoprotein that primarily conducts boundary lubrication between the joint surfaces. The combination of lubricin and hyaluronic acid can contribute to reduce distress and eliminate shear forces in synovial fluid.[28]

PRP injection in knee joint OA aims to build cartilage repair, reduce OA symptoms, and delay joint surgery.[29] PRP 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] The frequency of 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 the positive points for using it as knee joint OA treatment. Based on the pathophysiology and mechanism of PRP, clinically PRP is widely used to treat acute and chronic injuries or trauma. It results in high rate of wound healing and significant reduction in pain scale which can improve patient's quality of life. [5, 7]

5. Conclusion

The platelets rich plasma improves osteoarthritis related knee joint pain through the biological response through the nuclear factor kappa B (NFkB) pathway. The growth factors present in platelets rich plasma 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 platelets rich plasma in neurofibromatoses (NFB) deactivation are to lower chondrocyte inflammation, restore anabolic activity, and inhibit monocyte migration in order to prevent osteoarthritis progression and reduce pain.

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7. Declaration of interest

The Authors declare that there is no conflict of interest

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9. Authors' contribution

CT, Y: conception of the work, literature research, manuscript drafting

HBH: literature research, performed the analysis, manuscript editing

IP, VAP: literature research, manuscript reviewing and revising

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