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Platelet Rich Plasma (PRP) Injection in Osteoarthritis (OA) Knee

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ABSTRACT

Osteoarthritis (OA) is the most common degenerative joint disease in developing countries, including Indonesia. Although OA can affect all joints, the knee joint is the joint most commonly affected. The high prevalence of OA is due to increased life expectancy and the prevalence of obesity, which triggers chronic disability and increases social and economic burdens in developing countries. Treatment of knee OA is a challenge because the knee joint has low regenerative and recovery capabilities. Conservative therapies such as acetaminophen, non-steroidal anti-inflammatory drugs, and opioids are only effective in managing pain and reducing inflammation. One of the regenerative therapies currently being developed to treat knee OA is injection of platelet-rich plasma (PRP), which is an autologous blood product with high concentrations of platelets, growth factors, and cytokines. The use of PRP can be an alternative because it not only reduces inflammation, but has the ability to initiate and regenerate damaged tissue. However, even though PRP can be considered as a safe therapy for the treatment of knee OA, there are still pros and cons related to the technique used and the variation in the composition of the PRP used. This article will present the latest information regarding the mechanism and effectiveness of PRP in treating knee OA.

Keywords: *Knee osteoarthritis, Platelet Rich Plasma (PRP), regenerative therapy*

INTRODUCTION

Osteoarthritis (OA) of the knee is a progressive disease involving the tibial-femoral and patella-femoral intra-articular (IA) cartilages and all surrounding IA and periarticular structures (Laudy et al., 2015). This disease causes pain, loss of function, and inability to walk. OA most often affects adults to old age (elderly). OA alters normal joint metabolism favoring increased catabolism and decreased anabolism. Inflammation and vascular pathology, in combination with cell death, meniscal changes, bone remodeling and subchondral sclerosis, results in a vicious cycle of progressive joint degeneration. This can be exacerbated by excessive mechanical stress and oxidative damage. In addition, under conditions of metabolic or cytotoxic stress, such as in aging, autophagy may be upregulated, further decompensating homeostatic mechanisms (O'Connell et al., 2019).

In knee OA there is aging of the chondrocytes and loss of cartilage integrity. There is an increase in the moisture content of hyaline cartilage, accompanied by a corresponding decrease in the concentration, length and aggregation of proteoglycans,

leading to reduced cartilage stiffness and fibrillation of the cartilage surface. From here, the cartilage begins to wear away and deep fissures can form. Simultaneously, morphological changes in the subchondral bone were found. As synovial fluid infiltrates, subarticular cyst formation of the subchondral bone also occurs. Osteophytes (bony protrusions) are the hallmark of knee OA in areas of no stress, caused by flattening of the bone due to stress in areas of high wear and tear (Anzani, 2020).

OA of the hip and knee is ranked as the 11th highest contributor to global disability and the 38th highest in years lived with disability. The disability associated with OA of the knee carries a considerable economic burden, both directly related to treatment costs, especially joint replacement surgery and indirect costs related to work, including lost productivity. Knee OA affects between 6% and 40% of the general population and is increasing significantly among retired elite athletes, with prevalence rates as high as 95%. The global burden of knee OA, as assessed by WHO, is comparable to that of patients with cardiac dysrhythmias, liver cirrhosis, or stage IV renal disease.

In elderly patients, the main treatment for knee OA is knee replacement surgery. This is useful for relieving aches, pains, and improving function. Knee replacement surgery is chosen because of the limited age of joint replacement which is done with the use of implants. Referring to the American College of Rheumatology (ACR) guidelines, it is revealed that the treatment of knee OA includes non-pharmacological methods and pharmacological therapy. Non-pharmacological methods such as exercise and lifestyle modification are even better. While pharmacological therapy, for example, such as analgesics, administration of non-steroidal and steroidal anti-inflammatory drugs, and injection of corticosteroids. However, these treatments only provide temporary benefits and often have side effects (Siahaan & Suryawijaya, 2020). In addition, intra-articular injection therapy is also used as a good choice for the treatment of osteoarthritis. Platelet Rich Plasma (PRP) is an intra-articular therapy option that can be used.

LITERATURE REVIEW

Osteoarthritis (OA) Risk Factors

Age is a risk factor for OA, the older you get, the higher the chance of getting OA. It can be said that the risk factors for osteoarthritis in Indonesia will increase. Osteoarthritis has many risk factors including systemic risk factors and local risk factors. Systemic risk factors include age, sex, hormones, ethnicity, congenital and diet. While local risk factors include obesity, trauma, physical activity, work, mechanical factors and knee weakness. These risk factors will cause mechanical and chemical scars on the joint synovial which will stimulate the formation of abnormal molecules and cartilage degradation products that are in the joint synovial fluid. This process will lead to inflammation, damage to chondrocytes and pain in the joints (Anzani, 2020).

Cartilage hypertrophy may indicate osteoarthritis because it is related to the limited increase in macromolecular synthesis by chondrocytes to compensate for repair. This repair process is influenced by growth factors that control cell proliferation and communication between cells. Growth factors will induce chondrocytes to synthesize deoxyribonucleic acid (DNA) and proteins such as collagen and proteoglycans. Growth factors that play a role are insulin-like growth factor (IFG-1), growth factor, transforming growth factor b (TGF β), and colony stimulating factors (CSFs). IGF-1 plays an important role in the process of repairing joint cartilage and the sensitivity of cells to IGF-1 decreases when

inflammation occurs. TGF β has the effect of stimulating collagen and proteoglycan synthesis and suppressing stromelysin which is an enzyme that degrades proteoglycans, increases the synthesis of prostaglandin E2 (PGE2) and counteracts the inhibitory effect of PGE2 by interleukin 1 (IL-1). In making the diagnosis of OA, a reference is used in the form of criteria based on the American College of Rheumatology (ACR) criteria which divides OA into knee OA, hand OA and hip OA.

Osteoarthritis (OA) Diagnostic Criteria

Diagnostic criteria for OA of the hand are based clinically according to ACR, namely pain, aching or stiffness in the hand and at least 3 of the following criteria:

1. Hard tissue swelling of 2 or more of the following hand joints:
   - Distal joints of the 2nd and 3rd interphalanges
   - Proximal joints of the 2nd and 3rd interphalanges
   - The first joint of the carpometacarpophalangs of both hands
2. Hard tissue swelling of 2 or more distal interphalangeal joints
3. Less than 3 metacarpophalan joint swelling
4. Deformity of at least 1 in 10 joints of the hand in criterion 2 above

Diagnostic criteria for hip OA according to ACR are based on clinical and laboratory criteria, namely pain in the hip joint/coxae and at least one of the 2 groups of criteria below:

1. Hip internal rotation < 15º with ESR ≤ 45 mm/hour or hip flexion ≤ 115º (if ESR is difficult)
2. Internal rotation of the hip joint ≥ 15º with pain associated with internal rotation movements

The criteria for hip OA are based on clinical, laboratory and radiological criteria according to ACR, namely pain in the hip joint/coxae and at least 2 of the 3 criteria below:

1. LED < 20 mm in the first hour
2. Osteophytes on the femoral and/or acetabular radiographs
3. Radiological narrowing of the joint space

Platelet Rich Plasma (PRP)

PRP is an autologous blood product that contains growth factors and has a higher than normal concentration of platelets. For example, a normal platelet count is 150,000-450,000, it can be said to be PRP if the platelet count is 4-5 times above that level. The PRP preparation procedure begins with taking 27 ml of venous blood and then placing it into three 10 ml vacutainer tubes containing 0.106M sodium citrate. Then the blood was stirred carefully to combine with the anticoagulant, then the blood sample was centrifuged for 10 minutes at 3200rpm at 220C. The results of the centrifugation produce 3 layers, namely the inferior layer consisting of erythrocytes, the intermediate layer consisting of leukocytes, and the superior layer consisting of plasma (Gato-Calvo et al., 2019).

Then, the buffy coat and plasma layer were centrifuged again for 10 minutes at 1500 rpm to separate leukocytes. After that, the blood was centrifuged for the third time for 10 minutes at 3200 rpm to obtain 2 layers of plasma, namely the upper part consisting of platelet-poor plasma and the lower part, namely PRP. In OA of the knee, PRP injection aims to promote cartilage repair and relieve osteoarthritic symptoms, potentially delaying the need for joint replacement surgery. This therapy can be administered easily and without severe side effects to patients. Treated patients can

return to normal daily activity without difficulty immediately after infiltration (Ayhan et al., 2014).

When PRP is injected into an injured site, platelets are activated by endogenous thrombin or intra-articular collagen. Once activated, there will be secretion of growth factors and inflammatory mediators such as platelet derived growth factor (PDGF), interleukin-1 receptor antagonist (IL-1RA), soluble receptor of tumor necrosis factor (TNF-RI), tumor growth factor þ (TGF- þ), platelet factor 4 (PF4), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin growth factor (IGF), osteocalcin (Oc), osteonectin, fibrinogen, vitronectin, bronchectin and thrombospondin (Laudy et al., 2015).

IL-1 receptor antagonists inhibit the activation of the NFnB gene, a cytokine involved in the apoptotic process of inflammation. TGF-þ1 also acts as a factor that inhibits cartilage degradation, regulates and enhances the expression of the inhibitory tissue metalloproteinases (TIMP-1) gene. Other factors such as IGF-1, PDGF and TGF-favor support cartilage stabilization by controlling the metabolic functions of chondrocytes and subchondral bone, maintaining homeostasis between proteoglycan synthesis and degradation, and stimulating chondrocyte proliferation. Platelet growth factor can also stimulate synovial fibroblasts to synthesize hyaluronic acid.

The specific functions of several growth factors contained in PRP are as follows:

1. Transforming growth factor beta functions to stimulate undifferentiated mesenchymal cell proliferation, regulate endothelial, fibroblast and osteoblastic mitogenesis, regulate collagen synthesis and collagen secretion, regulate the mitogenic effects of other growth factors, inhibit macrophage and lymphocyte proliferation and stimulate endothelial chemotaxis and angiogenesis.
2. Basic fibroblast growth factor functions to support the growth and differentiation of chondroblasts and osteoblasts, is mitogenic for mesenchymal stem cells, chondrocytes and osteoblasts.
3. Platelet derived growth factor functions as a mitogenic for stem cells and osteoblasts, triggers chemotaxis and mitogenesis in fibroblasts or smooth muscle cells, regulates collagen secretion and collagen synthesis and stimulates neutrophil chemotaxis.
4. Epidermal endothelial growth factor functions to stimulate endothelial chemotaxis or angingogenesis, regulation of collagen secretion, stimulates epithelium or mesenchymal mitogenesis.
5. Vascular growth factor functions to increase angiogenesis and vascular permeability, stimulates mitogenesis for endothelial cells.
6. Connective tissue growth factor functions to support angiogenesis, cartilage regeneration, fibrosis and platelet adhesion (Blagojevic et al., 2010).

PRP in OA of the Knee

The use of PRP in the treatment of degenerative knee OA has increased in recent years given its high margin of safety and ease of manufacture and administration. Contrasting scientific evidence exists regarding PRP injection for knee OA, with the efficacy of PRP injection being widely reported. Improved effectiveness of PRP for the treatment of knee joint pain and function compared with HA or placebo and positive outcomes at all stages of knee OA (early, middle and late) have all been reported. In addition, the effect of PRP appears to last longer and is superior to that of

intramuscular injection therapy (Hussain et al., 2017). Comparisons between intra-articular PRP injection and placebo therapy and HA in mild and moderate knee OA generally show higher clinical outcome scores with PRP use. Similarly, using a meta-analysis to compare the efficacy of PRP injections with placebo or other therapeutic means for the treatment of knee OA have reported greater pain reduction and functional improvement with PRP use. However, this is at the expense of increasing nonspecific side effects.

The use of PRP has been advocated as a treatment option in all stages of knee OA. Intra-articular PRP injection in active patients with knee OA showed significant improvement in pain reduction, symptom improvement and quality of life. This may occur due to the immediate and prolonged release of growth factors, which promote healing resulting in a sustained clinical effect. Symptomatic relief for up to 12 months with increased benefit for patients with early degenerative changes of the knee has been found with significant improvement in function and reduction in pain with three injections per month producing significantly better outcomes in the short term. Improved pain outcomes after 3 months with a greater effect on lower OA rates have been reported. In moderate knee OA, functional status and pain improve with at least two injections. In end-stage knee OA, only one intra-articular injection of PRP may be needed for effective pain relief, thereby improving activities of daily living and QoL.

Mishra et al. trying to classify PRP into 2 parameters. The first is based on the presence or absence of white blood cells and their activation, while the second is based on the richness of the platelets. Another classification that is often used is the PAW classification system (Platelets, Activation, White cells), which consists of three variables, namely:

1. Absolute platelet concentration (P)
2. Activation method (A)
3. Relative presence or absence of white blood cells and neutrophils at baseline (Dohan Ehrenfest et al., 2014)

Different methods of producing PRP can give different products in composition and characteristics. Dohan Ehrenfest et al. illustrates that there are 3 methods to produce PRP, namely:

1. The double-spinning method will result in a 4-8 fold change in the platelet concentration above the baseline level as well as the leukocyte concentration.
2. The single-spinning method, will result in a 1-3 fold change in platelet concentration above the baseline level.
3. Selective blood filtration (Rezasoltani et al., 2017)

Based on the leukocyte and fibrin content, different PRP formulations can be divided into: Pure Platelet-Rich Plasma (P-PRP), Leukocyte-Platelet-Rich Fibrin (L-PRP), Pure Platelet-Rich Fibrin (P-PRF) and Platelet-Rich Fibrin (L-PRF) (Siahaan & Suryawijaya, 2020).

CONCLUSION

Various benefits were obtained from PRP as a biological autologous product in the treatment of knee osteoarthritis. In addition to the ease of administration and preparation, complications and side effects are also minimal, and has a wide range of therapeutic potential. Based on clinical research, PRP therapy is classified as safe and gives good results. However, further research is still needed regarding the consensus on the use of PRP for the recommended dose volume, dosing interval, and the need for activation or not, and if activation is needed, what type of method is

used. Possibly, not only differences in pathology of disease, but differences in disease severity are also needed to determine which type of PRP to use. But until now, clinicians who support the use of PRP consider the biological conditions that occur in patients and focus on the goals to be achieved by using PRP. In addition, patients must also be informed that even though the benefits obtained are quite good with minimal complications, PRP injection must still be considered.

Declaration by Authors

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REFERENCES

1. Anzani, B. P. (2020). Literature Review: Perbandingan Efektivitas Platelet Rich Plasma (PRP) dengan Asam Hialuronat (HA) sebagai Terapi Osteoarthritis. *Jurnal Kesehatan*, *11*(1), 158–166. https://doi.org/10.26630/jk.v11i1.1608
2. Ayhan, E., Kesmezacar, H., & Akgun, I. (2014). Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World Journal of Orthopedics*, *5*(3), 351–361. https://doi.org/10.5312/wjo.v5.i3.351
3. Blagojevic, M., Jinks, C., Jeffery, A., & Jordan, K. P. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *18*(1), 24–33. https://doi.org/10.1016/j.joca.2009.08.010
4. Dohan Ehrenfest, D. M., Andia, I., Zumstein, M. A., Zhang, C. Q., Pinto, N. R., & Bielecki, T. (2014). Classification of platelet concentrates (Platelet-Rich Plasma-PRP, platelet-rich fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: Current consensus, clinical implications and perspectives. *Muscles, Ligaments and Tendons Journal*, *4*(1), 3–9. https://doi.org/10.32098/mltj.01.2014.02
5. Gato-Calvo, L., Magalhaes, J., Ruiz-Romero, C., Blanco, F. J., & Burguera, E. F. (2019). Platelet-rich plasma in osteoarthritis treatment: Review of current evidence. *Therapeutic Advances in Chronic Disease*, *10*, 1–18. https://doi.org/10.1177/2040622319825567
6. Hussain, N., Johal, H., & Bhandari, M. (2017). An evidence-based evaluation on the use of platelet rich plasma in orthopedics - a review of the literature. *Sicot-J*, *3*(57), 1–7. https://doi.org/10.1051/sicotj/2017036
7. Laudy, A. B. M., Bakker, E. W. P., Rekers, M., & Moen, M. H. (2015). Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: A systematic review and meta-analysis. *British Journal of Sports Medicine*, *49*(10), 657–672. https://doi.org/10.1136/bjsports-2014-094036
8. O'Connell, B., Wragg, N. M., & Wilson, S. L. (2019). The use of PRP injections in the management of knee osteoarthritis. *Cell and Tissue Research*, *376*(1), 143–152. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L626374403%0Ahttp://dx.doi.org/10.1007/s00441-019-02996-x
9. Rezasoltani, Z., Taheri, M., Mofrad, M. K., & Mohajerani, S. A. (2017). Periarticular dextrose prolotherapy instead of intra-articular injection for pain and functional improvement in knee osteoarthritis. *Journal of Pain Research*, *10*, 1179–1187. https://doi.org/10.2147/JPR.S127633
10. Siahaan, Y. M. T., & Suryawijaya, N. (2020). Peran Terapi Regeneratif Platelet-Rich Plasma (PRP) pada Penanganan Osteoartritis Lutut. *Journal of Anaesthesia and Pain*, *1*(3), 18–27. https://doi.org/10.21776/ub.jap.2020.001.03.03

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