**Understanding Platelet-Rich Plasma as Potential Therapy To Improve Cardiac Function After Myocardial Infarction: Based On Evidence**

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**Short Running Title:** Platelet-Rich Plasma to Improve Cardiac Function

**ABSTRACT**

Myocardial infarction is the leading cause of death in the world’s population. The sudden and progressive loss of cardiomyocyte contractile cells due to infarction is disproportionate to the number of new cells formation. This pathological condition will ultimately reduce the function of the heart muscles. Platelet-rich plasma (PRP) in the last decade has been attracting attention regarding its role in cell regeneration. The content of cytokines and growth factors contained in PRP such as Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor Beta 1 (TGF-Β1), Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF), Basic Fibroblast Growth Factor (bFGF) and others are known to be involved in the migration, proliferation, and differentiation of various cell types and to induce post-ischemic angiogenesis. This review aims to analyze and investigate the benefits of PRP therapy in myocardial infarction. Recent literatures regarding the use of PRP in myocardial infarction was collected by searching PubMed and Google Scholar databases with the keywords of “Platelet-rich plasma”, “Myocardial Infarction”, “Reperfusion”, and “Angiogenesis”. The researches used was published between January 2011 and December 2022. Based on the results, Platelet-rich Plasma (PRP) is considered capable of accelerating angiogenesis, mitogenesis, protect cells from free radicals, reduce infarct area and scar tissue in myocardial infarction. PRP can also improve cardiac function in post myocardial infarction by increasing ejection fraction. In addition, PRP can also reduce treatment costs due to the risk of myocardial infarction complications such as bleeding and infection.

**Keywords**:

*Platelet-rich plasma, Myocardial infarction, Angiogenesis, Cardiac function*

**INTRODUCTION**

Myocardial infarction is the leading cause of death and premature mortality in the world's population.1 Myocardial infarction can destroy approximately 25% or one million cardiomyocytes in the left ventricle. There is a disproportion between sudden and progressive loss of contractile cells and the number of new cells formation. This condition caused by the reduced capacity of cells to replicate because of age. Therefore, ischemia or infarction will lead to pathological conditions such as myocyte hypertrophy and myocardial fibrosis. Cardiomyocyte cell regeneration can be achieved by implantation or by stimulation the capacity of endogenous cells to proliferate.2,3

Platelets are one source of *growth factors* involved in important processes, such as blood clots, immune response, angiogenesis, and cell proliferation in the body.4 After myocardial infarction occurs, platelets will release granules and microparticles that regulate: 1) The extravasation and accumulation of inflammatory cells in the myocardium after infarction; 2) The immunoactive response of leukocytes, especially neutrophils and monocytes/macrophages (M1) and activated M2 to regenerate tissue; 3) The activation and transformation of fibroblasts into myofibroblasts to synthesize Extracellular matrix (ECM); 4) The proliferation, migration and differentiation of cardiac progenitor cells; 5) The differentiation of progenitor cells into cardiomyocytes to enhance cardiac remodeling; 6) The increased inotropic activity of cardiomyocytes and the release of antiapoptotic signals.5

Platelet-rich plasma (PRP) is an autologous plasma taken from a blood sample and centrifuged to obtain a platelet-rich supernatant. PRP contains concentrates and platelets which can be activated by additional products such as calcium chloride, thrombin, or fibrinogen.6,7 Several studies regarding the role of PRP in cell regeneration in myocardial infarction have been conducted in the last decade. In addition, the use of PRP also attracts attention because of its economical reason, does not require complex tools and materials, and does not require trained experts. PRP is also a relatively non-invasive technique with low risk of infection and immunological reactions.8,9

**MATERIAL AND METHODS**

**Focused question**

The research question below was developed through the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) protocol: “What is the benefit of PRP in myocardial infarction?” and “What is the benefit of PRP to improve cardiac function after myocardial infarction?”

**Selection criteria**

The studies included in this review are: (1) Prospective clinical trials;(2) Animal studies;(3) Studies assessing PRP in patients with myocardial infarction; (4) The effect of PRP on cardiac function after myocardial infarction; (5) Researches in English. Articles in the form of Reviews, Case Reports and Case Series, Commentaries, Letters To The Editor, Short Communications wereexcluded.

**Search methodology**

In this article, we summarize the latest literatures regarding the use of PRP in myocardial infarction searched through PubMed and Google Scholar databases with the “Platelet-rich plasma”, “Myocardial Infarction”, “Reperfusion”, and “Angiogenesis” keywords*.* The research used is research published between January 2011 to December 2022. A summary of the search criteria and the use of MeSH *terms is* shown in table 1.

**Table 1.** Summary of MeSH terms,inclusion and exclusion criteria to filter the literature for this study

|  |  |  |
| --- | --- | --- |
| MeSH terms | Inclusion | Exclusion |
| “Platelet-rich plasma”  “Myocardial Infarction”  “Reperfusion”  “Angiogenesis” | (1) Prospective clinical trials | Review |
| (2) Animal studies | Case Report and Case Series |
| (3) Studies assessing PRP in patients with myocardial infarction | Commentaries |
| (4) Effects PRP on cardiac function after myocardial infarction | Letters To The Editor |
| 1. Research in English | Short Communications |

**RESULTS**

The benefits of PRP have been reported in various organs, but its specific efficacy in cases of myocardial infarction is still limited. After eliminating the same research, in our primary search we found 41 articles. Based on the abstract, title and exclusion criteria, 7 relevant articles were obtained which are described in table 2.

**Table 2.** Summary of the effect of Platelet-Rich Plasma (PRP) on myocardial infarction

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| NO | Author, year | Sample | Study Group | Duration | PRP Concentration | Route of Administration | Effect | Ref |
| 1. | Mishra *et al,* 2011 | Twenty eight mices | Four groups consisting of two treatments:   1. Permanent Ligation: Revaten PRP (n=5) and control group with 50 μl phosphate buffered saline (n=4) 2. Ischemia and Reperfusion: PRP (n=10) and control group with 50 μl of phosphate buffered saline (n = 9) | Seven days for group with Permanent Ligation and twenty-one days for group with ischemia and reperfusion | 50 µl PRP | Intramyocardium injection | Improved cardiac function (ejection fraction) after myocardial infarction. | 10 |
| 2. | Cheng *et al,* 2012 | Seventy eight wistar-kyoto female rats | Two groups:  Control (n=39) and PRP group (n=39) | Six weeks (observations were made on day 0, week 3 and week 6) | 150µl platelet gel: 75µl host plasma were mixed with 75µl pre-warmed DMEM | Intramyocardium injection | PRP caused de novo angiogenesis, producing more cardiomyocytes and endothelial cells and improve heart function. | 11 |
| 3. | Hargrave *et al*, 2012 | Eight white rabits | Two groups:  Control (n=3) and PRP group (n=5) | Two weeks | 200µl (0,21 mg) PRP per heart | Intramyocardium injection | PRP significantly reduced the size of the myocardial infarction area, improved post-infarction ventricular function, decreased production Reactive Oxygen Species (ROS), and decreased mitochondrial depolarization | 12 |
| 4. | Vu *et al*, 2015 | Thirthy Yorkshire female pigs (65-70 kg) | Five groups: 1) Hyaluronic acid-based hydrogel (n=6); 2) autologous platelet-rich plasma (PRP) (n=6); 3) ascorbic acid-enriched hydrogel (50 mg/L), combined with IV ibuprofen (25 mg/kg) and allopurinol (25 mg/kg) (cocktail group) (n=6); 4) PRP and cocktail (full-compound) (n=6); or 5) saline (control) (n=6). | Eight weeks | 8 ml PRP | Intramyocardium injection | PRP can reduce scar tissue in the left ventricle after infarction, inhibit the expansion of infarct size and promote the formation of new blood vessels. | 13 |
| 5. | Hehanusa *et al*, 2019 | Mononuclear cell | Three groups: 1) PRP group; 2) PPP group (0.5 mL); 3) Control. | Two weeks | 0,5 mL PRP | In vitro | Significantly increased myocardial endothelial progenitor cell growth | 14 |
| 6. | Suryawan *et al*, 2020 | Adipose derived Mesenchymal Stem Cell | Three groups: 1) negative control group (α-mem medium-no fluorescence); 2) Positive control group (Cardiomyogenic kit medium-with fluorescence); 3) The PRP group | Two weeks | 5x109 /L PRP | In vitro | PRP was able to accelerate the differentiation of Adipose derived Mesenchymal Stem Cells into cardiomyocytes | 15 |
| 7. | Torabi *et al*, 2020 | Human-Induced Pluripotent Stem Cells (iPSCs) | Two groups: the control group with 5mL phosphate buffered saline and the PRP group. | Four weeks | 5 ml PRP | In vitro | PRP can accelerate the differentiation of Human-Induced Pluripotent Stem Cells (iPSCs) into cardiomyocytes. | 16 |

**DISCUSSION**

Platelet-rich plasma (PRP) is a platelet-rich product resulting from blood centrifugation which can be activated ifcombined with calcium chloride, thrombin or fibrinogen*.*17 The number of platelets occured in PRP was 4,410±34x103, higher than Platelet-Poor Plasma (PPP) (p < 0.005) and found to be 250% more in numbers than platelets in whole blood preparations.18,19 PRP that consists of 15 ml/kg (equivalent to 2.0 x 1010 platelets/kg) can increase circulating platelets by about 40% (p = 0.03).20

Although the molecular mechanism is unclear, PRP is known to be involved in the migration, proliferation, and differentiation of various cell types.21,22 This is associated with several cytokines and growth factors contained in PRP, such as Platelet-Derived Growth Factor (PDGF) which stimulates the formation of type I collagen and triggers the process of angiogenesis; Transforming Growth Factor Beta 1 (TGF-Β1) which stimulates the proliferation and differentiation of stem mesenchymal cells, synthesis the type I collagen, and triggers the angiogenesis; Epidermal Growth Factor (EGF) which stimulates tissue granulation; Vascular Endothelial Growth Factor (VEGF) which induces endothelial cell chemotaxis and proliferation, triggers angiogenesis, prompts vascular hyperpermeability, and precipitate renal stem cell differentiation; Basic Fibroblast Growth Factor (b-FGF) that induces post-ischemic angiogenesis; Insulin-Like Growth Factor (IGF) which promotes angiogenesis and myogenesis; Platelet Factor 4 (PF4); Adenosine Triphosphate (ATP); Adenosine Diphosphate (ADP); Angioprotein-2; Fibronectin; Osteocalcin; Serotonin; and Thrombospondin-1 (TSP-1), and others.17,23,24,25 Furthermore, the presence of leukocytes and interleukins in PRP play important role in its antimicrobial effect.26

The most common growth factor in PRP due its concentrations were TGF-β1 (30,500±20,500 pg/ml), followed by PDGF-BB (9440±1620 pg/ml), VEGF (2040±971 pg/ml), EGF (906±206 pg/ml) and bFGF (32.6±8.7 pg/ml).27 The mean value of VEGF in PRP was found to be higher than normal plasma/serum and when compared with the control group receiving saline solution, the value was 1.42 times higher (p = 0.017).28,29 The study of protocol preparation of PRP reported that the release of VEGF, EGF, bFGF, IL-17, and IL-8 were significantly higher when PRP was incubated at 4°C before coagulated. This cold temperature also increases the activation of p38 which is involved in the process of angiogenesis.30

Research on PRP in organs has been widely carried out. PRP with saline solution can increase 25-50% angiogenesis and regeneration in wound healing process.31 In 56 patients with chronic diabetic ulcers, a significant healing process occurred in PRP-treated group compared to control group (86% vs 68%).32 Based on color, surface appearance, hair growth and wound drying, better healing was found in the combination of PRP and Stromal Vascular Fraction (SVF).33 Patients with thromboangiitis obliterans also experienced a decrease in their VAS Score around 50% since 24 hours of giving PRP (Mean VAS Score 4.35).34

Platelets injection post-infarction increase the number of cardiomyocytes and endothelial cells, thereby promoting mitogenesis and angiogenesis. Within 7 days of observation, mature blood vessels were found in the PRP group.11 This new blood vessel formation was found not only in the infarcted area but also significantly in the peri-infarction area.13

Infarction area in PRP-treated rabbit model was found to be smaller than in the control group (p < 0.05).12 Confirmed by histopathological analysis, scar tissue was also found to be more abundant in the control group with phosphate-buffered saline than in the PRP group.10 Through the examination of flow cytometry, PRP was able to significantly reduce ROS production in H9c2 cells at concentrations of 44 mM (p<0.05) and 8.8 mM (p<0.05). Decreased ROS production cause a decrease in mitochondrial depolarization, which often used as a marker of apoptosis in nucleated and non nucleated cells. Thus, PRP was said to protect heart muscle from expanding ischemic areas.12, 35 The combination of PRP with antioxidants and anti-inflammatories also resulted in a lighter left ventricular mass post-infarction than the control group (196±15 g vs 269±20 g; p<0.05).13 Evidence of reduced infarct area was also found in ischemic stroke cases where the volume reduction was significant in the PRP group (31%±2.7%; p<0.05).36

Cardiomyocyte cells will die and undergo necrosis after myocardial infarction. Then, these necrotic cardiomyocytes will be gradually replaced by noncontractile fibroblasts, thus interfering with cardiac function.37, 38 PRP was found to increase the Left Ventricular Ejection Fraction (LVEF)and to decrease the exacerbation of inflammation after myocardial infarction.11 Administration of PRP for 7 days in rats whose anterior descending artery was ligated could increase LVEF by 38% (p=0.27), whereas administration of PRP for 21 days in groups of rats undergoing post-ischemic reperfusion therapy could increase LVEF by 28% (p = 0.038).10 Administration of PRP therapy in mice with myocardial infarction also showed tissue protection, endogenous regeneration, greater capillary density, and lower myocyte hypertrophy than the control group.11

The risk of bleeding can occur in patients after myocardial infarction due to anti-platelet consumption.39 Studies in animals receiving the anti-platelet vorapaxar, aspirin, and clopidogrel have shown that PRP reduces the risk of bleeding by reducing bleeding times by 150 seconds after treatment.40 Another advantage of PRP can be judged by its safety. A retrospective study involving 611 patients post cardiac stenting (post myocardial infarction), diabetes mellitus, stroke, osteoarthritis, anti-aging, hypertension, etc., did not find any side effects such as allergies, infections, and coagulation problems in patients receiving PRP therapy.41 Leukocytes and cytokines contained in PRP can reduce the risk of Deep Sternal Wound Infection (DSWI) by 7.41% and inhibit the growth of bacteria Staphylococcus aureus.42 Another role of PRP was also found in patients with severe COVID-19 symptoms where there was a significant decrease in CRP levels (p = 0.005).43

PRP also shows its existence as a protective factor against free radicals. The levels of Reactive Oxygen Species (ROS) and pro-inflammatory cytokines in cases of skin trauma can be reduced by PRP by decreasing the expression of pASK-1 and pNF-KB.44 Decreased total oxidant status, oxidative stress index, and ischemic score on histopathological results of ovarian torsion in rats were found after PRP administration.45 In addition, this cytoprotective effect was also reported in cases of testicular torsion in ratsin which there is a decrease of nitric oxide (NO), IL1B,TNF-α,caspase 3; and increased CAT, GST, GSH, and BCL2 as evidenced by histological improvement.26

The use of PRP has so far been limited due to its short half-life. After PRP was purified and injected, within 5-7 days its effect disappeared because PRP is easily broken down in the blood vessels and excreted. Therefore, several studies have found that the single use of PRP is less effective in promoting angiogenesis and recommends its combination with other preparations such as gelatin hydrogel to prolong the duration of action.46 This combination is reported to be much more potent and effective for restoring blood perfusion in ischemic conditions.47

Although many studies support the benefits of using PRP, one study reported that administration of PRP can increase the ischemic area of ​​renal tissue. This condition was confirmed by histopathological examination, ultrasound renal flow parameters, serum creatinine levels, urea levels, renal mass and volume. Several hypotheses have been proposed to support this situation, namely: (1) The possibility of thrombus in intrarenal vessels; (2) The damage occurred due to the higher osmolarity of PRP compared to saline solution in the control group; (3) The injected PRP also releases cytokines and leukocytes (Mean 5300 ±3600/μL) along with growth factors, thereby worsening the work of the kidneys; (4) The PRP used induces an immune reaction because it is taken from another mouse sample; (5) PRP injection when the kidney is still ischemic has the potential to cause compartment syndrome; (6) This study is the first study on the kidney, so it is suspected that PRP is not effectively applied to solid organs.48

**CONCLUSION**

Platelet-rich Plasma (PRP) isconsidered capable of accelerating angiogenesis, mitogenesis, protecting cells from free radicals, reducing infarct area and scar tissue in myocardial infarction. PRP can also improve cardiac function by increasing ejection fraction in post-myocardial infarction cases. In addition to the clinical benefits, PRP also provides economic benefits because it can reduce medical costs due to the risk of complications of myocardial infarction such as bleeding and infection. Despite its limitations related to its short half-life and other controversies, the potential use of PRP as a modality for the treatment of myocardial infarction should be further investigated.

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