Indexed by : DOAJ Google Crossref Dimension sinta GARUDA

J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Review Article

Understanding Platelet-Rich Plasma as Potential Therapy to Improve Cardiac Function after Myocardial Infarction: Based on the in-vitro and animal model evidence

Linda Chiuman[1], Dearni Anggita Krismayani Purba[2], Hendy Million Samin[3*]

[1]Department of Biomedical Science, Faculty of Medicine, Prima Indonesia University, Indonesia
[2]Faculty of Medicine, University of North Sumatra, Indonesia
[3] Faculty of Medicine, Prima Indonesia University, Indonesia

Article Info
History
Received: 09 Feb 2023
Accepted: 14 Apr 2023
Available: 30 Apr 2023

Abstract
Myocardial infarction is the leading cause of death in the world's population. The cardiac remodeling and disproportion of the loss and the new formation of contractile cells will ultimately reduce the function of the heart muscles after infarction. Platelet-rich plasma (PRP) in the last decade has been attracted 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-B1), 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 researchers used was published between January 2011 and December 2022. Based on the in-vitro and animal model evidence, platelet-rich plasma (PRP) is considered capable of accelerating angiogenesis and mitogenesis, protecting cells from free radicals, reducing infarct area and scar tissue in myocardial infarction, and also increasing ejection fraction.

Keywords:
Platelet-rich plasma; Myocardial infarction; Angiogenesis; Cardiac function
Permalink/ DOI: https://doi.org/10.14710/jbtr.v9i1.17379

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. The cardiac remodeling that happens after infarction and the disproportion of the loss and the new formation of contractile cells will ultimately reduce the function of the heart muscles.[2] Cardiac remodeling is defined as the volume increase of the left ventricular cavity with a reduced LV ejection fraction following myocardial infarction. The hemodynamic overload activates maladaptive remodeling cascade, resulting in compensatory left ventricle hypertrophy. On the other hand, cytokine release and inflammation lead to fibroblast proliferation and metalloproteinase activation cause fibrosis.[3] 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 essential processes, such as blood clots, immune response, angiogenesis, and cell proliferation in the body.[4]

* Corresponding author:
E-mail: *hendy.samin1988@gmail.com*
(Hendy Million Samin)

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 of PRP on cardiac function after myocardial infarction	Letters to the Editor
	(5) Research in English	Short communications

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; 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 economic 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

This study aims to review the beneficial effect of PRP in myocardial infarction systematically. The research question 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 systematic 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) research in English. Articles in the form of reviews, case reports and case series, commentaries, letters to the editor, short communications were excluded.

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.

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.

DISCUSSION

PRP is a platelet-rich product resulting from blood centrifugation which can be activated if combined with calcium chloride, thrombin, or fibrinogen.[17] The number of platelets that occurred in PRP was $4{,}410 \pm 34 \times 10^3$, 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 containing 15 ml/kg (equivalent to 2.0×10^{10} 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] PRP can accelerate the differentiation of Human-Induced Pluripotent Stem Cells (iPSCs) into cardiomyocytes.[16] Suryawan, 2020 reported that GATA-4 expression in PRP-administered AMSCs was found to be higher compared to negative and positive controls (67.04 ± 4.49 vs 58.15 ± 1.23 $p < 0.05$; 67.04 ± 4.49 vs 52.96 ± 2.02 $p < 0.05$). GATA-4 is a specific transcription factor indicating cardiomyocyte development in the cardiac progenitor formation phase. The finding was supported by immunocytochemical results on troponin expression, which showed a marked increase in the PRP group compared to negative and positive controls (38.13 ± 5.2 vs 10.73 ± 2.39 $p<0.05$; 38.13 ± 5.2 vs 26.00 ± 0.4 $p<0.05$). [15] This study supports previous flow cytometry analysis confirming that cardiac progenitor cells (CPC) and AMSCs express the same markers CD90 and CD105.[23] Several previous attempts have been made to facilitate AMSCs, such as the administration of 5-azacytidine, and the result was that 5-azacytidine was insufficient in supporting AMSCs to differentiate into cardiomyocytes fully.[24] However, since this is the first study of PRP on AMSCs, it still needs further investigation.

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	Intramyocardial 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	Intramyocardial injection	PRP caused de novo angiogenesis, producing more cardiomyocytes and endothelial cells and improve heart function.	11
3.	Hargrave *et al*, 2012	Eight white rabbits	Two groups: Control (n=3) and PRP group (n=5)	Two weeks	200µl (0,21 mg) PRP per heart	Intramyocardial 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	Thirty 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	Intramyocardial 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

Several PRP cytokines and growth factors that have been proposed as the underlying mechanism, 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-B1) 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

Table 2. Continuous..

No	Author, year	Sample	Study Group	Duration	PRP Concentration	Route of Administration	Effect	Ref
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	$5x10^9$ /L PRP	In vitro	PRP-administered group had a higher adipose derived mesenchymal stem cells (AMSCs) differentiation rate into cardiomyocytes than the positive and negative control groups.	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

myogenesis; platelet factor 4 (PF4); adenosine triphosphate (ATP); adenosine diphosphate (ADP); angioprotein-2; fibronectin; osteocalcin; serotonin; and thrombospondin-1 (TSP-1), and others.[17,25] Furthermore, the presence of leukocytes and interleukins in PRP play essential role in its antimicrobial effect.[26]

The most common growth factor in PRP due to its concentrations was 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 higher than expected plasma/serum; compared to 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 the 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% within 24 hours after PRP was given (mean VAS score 4.35).[34]

Post-infarction platelets injection increases the number of cardiomyocytes and endothelial cells, thereby promoting mitogenesis and angiogenesis. Within seven 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]

The infarction area in the 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 causes a decrease in mitochondrial depolarization, which is often used as a marker of apoptosis in nucleated and non-nucleated cells. Thus, PRP was said to protect the 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]

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.[36, 37] 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% ($p=0.27$). In contrast, the 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.[38]

Studies in animals receiving the anti-platelet vorapaxar, aspirin, and clopidogrel have shown that PRP reduces bleeding risk by reducing bleeding times by 150 seconds after treatment.[39] 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., found no side effects such as allergies, infections, and coagulation problems in patients receiving PRP therapy.[40,41]

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.[42] Decreased total oxidant status, oxidative stress index, and ischemic score on histopathological results of ovarian torsion in rats were found after PRP administration.[43] In addition, this cytoprotective effect was also reported in cases of testicular torsion in rats in 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, its effect disappeared within 5-7 days 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. This combination is reported to be much more potent and effective for restoring blood perfusion in ischemic conditions.[18,44]

Although many studies support the benefits of using PRP, one study reported that administration of PRP could increase the ischemic area of renal tissue. Histopathological examination, ultrasound renal flow parameters, serum creatinine levels, urea levels, renal mass and volume confirmed this condition. 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.[45]

CONCLUSION

Platelet-rich plasma (PRP) is considered capable of accelerating angiogenesis and mitogenesis, protecting cells from free radicals, reducing infarct area and scar tissue in myocardial infarction, and also increasing ejection fraction. However, this review is based on in-vitro and animal model evidence; it remains unknown in humans. The potential use of PRP as a modality to improve cardiac function after myocardial infarction should be further investigated.

ACKNOWLEDGEMENTS

Thank you to all parties who have facilitated and assisted in this review, especially to Dr. dr. Linda Chiuman, MKM for her guidance on this manuscript.

REFERENCES

1. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SK, AlKatheeri R, Alblooshi FM, Almatrooshi ME, Alzaabi ME, Al Darmaki RS, Lootah SN. Global epidemiology of ischemic heart disease: Results from the global burden of disease study. Cureus. 2020 Jul;12(7). DOI: https://doi.org/10.7759/cureus.9349
2. Giacca M. Cardiac regeneration after myocardial infarction: an approachable goal. Current Cardiology Reports. 2020 Oct;22(10):1-8. DOI: https://doi.org/10.1007/s11886-020-01361-7 PMid:32778947 PMCid: PMC7417409
3. Schirone L, Forte M, Palmerio S, Yee D, Nocella C, Angelini F, Pagano F, Schiavon S, Bordin A, Carrizzo A, Vecchione C. A review of the molecular mechanisms underlying the development and progression of cardiac remodeling. Oxidative medicine and cellular longevity. 2017 Oct;2017. https://doi.org/10.1155/2017/3920195 PMid:28751931 PMCid: PMC5511646
4. Le AD, Enweze L, DeBaun MR, Dragoo JL. Current clinical recommendations for use of platelet-rich plasma. Current reviews in musculoskeletal medicine. 2018 Dec; 11:624-34. DOI: https://doi.org/10.1007/s12178-018-9527-7 PMid:30353479 PMCid: PMC6220007
5. Walsh TG, Poole AW. Do platelets promote cardiac recovery after myocardial infarction: roles beyond occlusive ischemic damage. American Journal of Physiology-Heart and Circulatory Physiology. 2018 May 1;314(5):H1043-8. DOI: https://doi.org/10.1152/ajpheart.00134.2018 PMid:29547023 PMCid: PMC6008147
6. Lee JW, Kwon OH, Kim TK, Cho YK, Choi KY, Chung HY, et al. Platelet-rich plasma: quantitative assessment of growth factor levels and comparative analysis of activated and inactivated groups. Archives of plastic surgery. 2013; 40(5):530-5. DOI: https://doi.org/10.5999/aps.2013.40.5.530 PMid:24086805 PMCid: PMC3785585
7. Andia I, Abate M. Platelet-rich plasma: underlying biology and clinical correlates. Regenerative medicine. 2013 Sep;8(5): 645-58.DOI: https://doi.org/10.2217/rme.13.59 PMid: 23998756
8. De Pascale MR, Sommese L, Casamassimi A, Napoli C. Platelet derivatives in regenerative medicine: an update. Transfusion medicine reviews. 2015 Jan 1;29(1): 52-61. DOI: https://doi.org/10.1016/j.tmrv.2014.11.001 PMid:25544600
9. Burnouf T, Strunk D, Koh MB, Schallmoser K. Human platelet lysate: replacing fetal bovine serum as a gold standard for human cell propagation? Biomaterials. 2016 Jan 1; 76:371-87. DOI: https://doi.org/10.1016/j.biomaterials.2015.10.065 PMid:26561934

10. Mishra A, Velotta J, Brinton TJ, Wang X, Chang S, Palmer O, Sheikh A, Chung J, Yang PC, Robbins R, Fischbein M. RevaTen platelet-rich plasma improves cardiac function after myocardial injury. Cardiovascular Revascularization Medicine. 2011 May 1;12(3):158-63. DOI: https://doi.org/10.1016/j.carrev.2010.08.005 PMid:21122486
11. Cheng K, Malliaras K, Shen D, Tseliou E, Ionta V, Smith J, Galang G, Sun B, Houde C, Marbán E. Intramyocardial injection of platelet gel promotes endogenous repair and augments cardiac function in rats with myocardial infarction. J Am Coll Cardiol. 2012 Jan 17;59(3):256-64. DOI: https://doi.org/10.1016/j.jacc.2011.10.858 PMid: 22240131 PMCid: PMC3581074
12. Matsui M, Tabata Y. Enhanced angiogenesis by multiple release of platelet-rich plasma contents and basic fibroblast growth factor from gelatin hydrogels. Acta biomaterialia. 2012 May 1;8(5):1792-801. DOI: https://doi.org/10.1016/j.actbio.2012.01.016 PMid: 22293581
13. Vu TD, Pal SN, Ti LK, Martinez EC, Rufaihah AJ, Ling LH, Lee CN, Richards AM, Kofidis T. An autologous platelet-rich plasma hydrogel compound restores left ventricular structure, function and ameliorates adverse remodeling in a minimally invasive large animal myocardial restoration model: a translational approach: Vu and Pal "Myocardial Repair: PRP, Hydrogel and Supplements". Biomaterials. 2015 Mar 1; 45:27-35. DOI: https://doi.org/10.1016/j.biomaterials.2014.12.013 PMid: 25662492
14. Hehanusa RR, Andrianto A, Pikir BS. Effect of Platelet Rich Plasma on Proliferation of Endothelial Progenitor Cell (EPC) of Stable Coronary Artery Disease Patient. Indonesian Journal of Cardiology. 2019 Sep 11;40(2). DOI: https://doi.org/10.30701/ijc.v40i2.851
15. Suryawan IG, Andrianto A, Anggaraeni AD, Agita A, Nugraha RA. The Role of Human Platelet-Rich Plasma to Enhance the Differentiation from Adipose derived Mesenchymal Stem Cells into Cardiomyocyte: An Experimental Study. bioRxiv. 2021 Jan 1:2020-12. DOI: https://doi.org/10.1101/2020.12.10.420679
16. Torabi M, Abazari MF, Zare Karizi S, Kohandani M, Hajati-Birgani N, Norouzi S, Nejati F, Mohajerani A, Rahmati T, Mokhames Z. Efficient cardiomyocyte differentiation of induced pluripotent stem cells on PLGA nanofibers enriched by platelet-rich plasma. Polymers for Advanced Technologies. 2021 Mar;32(3):1168-75. DOI: https://doi.org/10.1002/pat.5164
17. Ozcelik U, Ekici Y, Bircan HY, Aydogan C, Turkoglu S, Ozen O. Effect of topical plateletrich plasma on burn healing after partial-thickness burn injury. Med Sci Monit. 2016;22:1903-9. DOI: https://doi.org/10.12659/MSM.895395 PMid: 27262706 PMCid: PMC4913826
18. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: new performance understandings and therapeutic considerations in 2020. International journal of molecular sciences. 2020 Oct 21;21(20):7794. DOI: https://doi.org/10.3390/ijms21207794 PMid:33096812 PMCid: PMC7589810
19. Karina KA, Sobariah S, Rosliana I, Rosadi I, Widyastuti T, Afini I, Wanandi SI, Soewondo P, Wibowo H, Pawitan JA. Evaluation of platelet-rich plasma from diabetic donors shows increased platelet vascular endothelial growth factor release. Stem cell investigation. 2019;6. DOI: https://doi.org/10.21037/sci.2019.10.02 PMid: 32039265 PMCid: PMC6987324
20. Cai TQ, Wickham LA, Sitko G, Michener MS, Raubertas R, Handt L, Chintala M, Seiffert D, Forrest M. Platelet transfusion reverses bleeding evoked by triple anti-platelet therapy including vorapaxar, a novel platelet thrombin receptor antagonist. European journal of pharmacology. 2015 Jul 5; 758:107-14. DOI: https://doi.org/10.1016/j.ejphar.2015.03.073 PMid:25857224
21. Alsousou J, Ali A, Willett K, Harrison P. The role of platelet-rich plasma in tissue regeneration. Platelets. 2013 May 1;24(3):173-82. DOI: https://doi.org/10.3109/09537104.2012.684730 PMid:22647081
22. Rosadi I, Karina K, Rosliana I, Sobariah S, Afini I, Widyastuti T, Barlian A. In vitro study of cartilage tissue engineering using human adipose-derived stem cells induced by platelet-rich plasma and cultured on silk fibroin scaffold. Stem cell research & therapy. 2019 Dec;10(1):1- 5. DOI: https://doi.org/10.1186/s13287-019-1443-2 PMid: 31801639 PMCid: PMC6894137
23. Yee-Goh AS, Yamauchi A, van Hout I, Bellae Papannarao J, Sugunesegran R, Parry D, Davis P, Katare R. Cardiac Progenitor Cells and Adipocyte Stem Cells from Same Patients Exhibit In Vitro Functional Differences. International Journal of Molecular Sciences. 2022 May 17;23(10):5588. DOI: https://doi.org/10.3390/ijms23105588 PMid:35628402 PMCid: PMC9141982
24. Malandraki-Miller S, Lopez CA, Al-Siddiqi H, Carr CA. Changing metabolism in differentiating cardiac progenitor cells-can stem cells become metabolically flexible cardiomyocytes? Frontiers in cardiovascular medicine. 2018 Sep 19; 5:119. DOI: https://doi.org/10.3389/fcvm.2018.00119 PMid:30283788 PMCid: PMC6157401
25. Oh JH, Kim WO, Park KU, Roh YH. Comparison of the cellular composition and cytokine-release kinetics of various platelet-rich plasma preparations. The American journal of sports medicine. 2015 Dec;43(12):3062-70. DOI: https://doi.org/10.1177/0363546515608481 PMid:26473014
26. Samy A, El-Adl M, Rezk S, Marghani B, Eldomany W, Eldesoky A, Elmetwally MA. The potential protective and therapeutic effects of platelet-rich plasma on ischemia/reperfusion injury following experimental torsion/detorsion of testis in the

Albino rat model. Life sciences. 2020 Sep 1; 256:117982. DOI: https://doi.org/10.1016/j.lfs.2020.117982 PMid: 32562693

27. Matsui M, Tabata Y. Enhanced angiogenesis by multiple release of platelet-rich plasma contents and basic fibroblast growth factor from gelatin hydrogels. Acta biomaterialia. 2013 May 1;8(5):1792-801. DOI: https://doi.org/10.1016/j.actbio.2012.01.016 PMid: 22293581
28. Karina K, Biben JA, Ekaputri K, Rosadi I, Rosliana I, Afini I, Widyastuti T, Sobariah S, Subroto WR. In vivo study of wound healing processes in Sprague-Dawley model using human mesenchymal stem cells and platelet-rich plasma. Biomedical Research and Therapy. 2021 Apr 30;8(4):4316-24. DOI: https://doi.org/10.15419/bmrat.v8i4.670
29. Moog P, Kirchhoff K, Bekeran S, Bauer AT, von Isenburg S, Dornseifer U, Machens HG, Schilling AF, Hadjipanayi E. Comparative evaluation of the angiogenic potential of hypoxia preconditioned blood-derived secretomes and platelet-rich plasma: An in vitro analysis. Biomedicines. 2020 Jan;8(1):16. DOI: https://doi.org/10.3390/biomedicines8010016 PMid: 31963131 PMCid: PMC7168246
30. Etulain J, Mena HA, Meiss RP, Frechtel G, Gutt S, Negrotto S, Schattner M. An optimised protocol for platelet-rich plasma preparation to improve its angiogenic and regenerative properties. Scientific reports. 2018 Jan 24;8(1):1-5. DOI: https://doi.org/10.1038/s41598-018-19419-6 PMid: 29367608 PMCid: PMC5784112
31. Oneto P, Zubiry PR, Schattner M, Etulain J. Anticoagulants interfere with the angiogenic and regenerative responses mediated by platelets. Frontiers in bioengineering and biotechnology. 2020 Mar 20; 8:223. DOI: https://doi.org/10.3389/fbioe.2020.00223 PMid: 32266247 PMCid: PMC7098916
32. Ahmed M, Reffat SA, Hassan A, Eskander F. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. Annals of vascular surgery. 2017 Jan 1; 38:206-11. DOI: https://doi.org/10.1016/j.avsg.2016.04.023 PMid: 27522981
33. Karina MF, Rosadi I, Afini I, Widyastuti T, Sobariah S, Remelia M, Puspitasari RL, Rosliana I, Tunggadewi TI. Combination of the stromal vascular fraction and platelet-rich plasma accelerates the wound healing process: pre-clinical study in a Sprague-Dawley rat model. Stem cell investigation. 2019;6. DOI: https://doi.org/10.21037/sci.2019.06.08 PMid: 31463311 PMCid: PMC6691081
34. Sharma D, Agarwal P, Jain S, Kothari R. Autologous platelet-rich plasma for treatment of ischemic ulcers in buerger's disease: A pilot study with short-term results. Indian Journal of Vascular and Endovascular Surgery. 2018 Jan 1;5(1):14. DOI: https://doi.org/10.4103/ijves.ijves_47_17
35. Gyulkhandanyan AV, Allen DJ, Mykhaylov S, Lyubimov E, Ni H, Freedman J, Leytin V. Mitochondrial Inner Membrane Depolarization as a Marker of Platelet Apoptosis: Disclosure of Nonapoptotic Membrane Depolarization. Clin Appl Thromb Hemost. 2017 Mar;23(2):139-147. DOI: https://doi.org/10.1177/1076029616665924 PMid: 27637909
36. Hirt MN, Hansen A, Eschenhagen T. Cardiac tissue engineering: state of the art. Circulation research. 2014 Jan 17;114(2):354-67. DOI: https://doi.org/10.1161/CIRCRESAHA.114.300522 PMid: 24436431
37. Goradel NH, Hour FG, Negahdari B, Malekshahi ZV, Hashemzehi M, Masoudifar A, Mirzaei H. Stem cell therapy: a new therapeutic option for cardiovascular diseases. Journal of cellular biochemistry. 2018 Jan;119(1):95-104. DOI: https://doi.org/10.1002/jcb.26169 PMid: 28543595
38. Mullen L, Meah MN, Elamin A, Aggarwal S, Shahzad A, Shaw M, Hasara J, Rashid M, Fisher M, Ali T, Patel B. Risk of Major Bleeding with Potent Antiplatelet Agents After an Acute Coronary Event: A Comparison of Ticagrelor and Clopidogrel in 5116 Consecutive Patients in Clinical Practice. Journal of the American Heart Association. 2021 Apr 20;10(8): e019467. DOI: https://doi.org/10.1161/JAHA.120.019467 PMid: 33834845 PMCid: PMC8174168
39. Cai TQ, Wickham LA, Sitko G, Michener MS, Raubertas R, Handt L, Chintala M, Seiffert D, Forrest M. Platelet transfusion reverses bleeding evoked by triple anti-platelet therapy including vorapaxar, a novel platelet thrombin receptor antagonist. European journal of pharmacology. 2015 Jul 5; 758:107-14. DOI: https://doi.org/10.1016/j.ejphar.2015.03.073 PMid: 25857224
40. Karina K, Ekaputri K, Biben JA, Purwoko RH, Sibuea TP, Astuti SL, Loho AM, Limengka Y, Agustini S, Krisandi G, Maryam A. Evaluating the Safety of Intravenous Delivery of Autologous Activated Platelet-rich Plasma. Journal of Health Sciences. 2020. DOI: https://doi.org/10.17532/jhsci.2021.1276
41. Patel AN, Selzman CH, Kumpati GS, McKellar SH, Bull DA. Evaluation of autologous platelet rich plasma for cardiac surgery: outcome analysis of 2000 patients. Journal of cardiothoracic surgery. 2016 Dec;11(1):1-6. DOI: https://doi.org/10.1186/s13019-016-0452-9 PMid: 27068030 PMCid: PMC4828785
42. Rah DK, Min HJ, Kim YW, Cheon YW. Effect of platelet-rich plasma on ischemiareperfusion injury in a skin flap mouse model. International journal of medical sciences. 2017;14(9):829 DOI: https://doi.org/10.7150/ijms.19573 PMid: 28824320 PMCid: PMC5562190
43. Bakacak M, Bostanci MS, İnanc F, Yaylali A, Serin S, Attar R, Yildirim G, Yildirim OK. Protective effect of platelet rich plasma on experimental ischemia/reperfusion injury in rat ovary.

Gynecologic and obstetric investigation. 2016;81(3):225-31.
DOI: https://doi.org/10.1159/000440617 PMid: 26496072

44. Kim YH, Furuya H, Tabata Y. Enhancement of bone regeneration by dual release of a macrophage recruitment agent and platelet-rich plasma from gelatin hydrogels. Biomaterials. 2014 Jan 1;35(1):214-24.
DOI: https://doi.org/10.1016/j.biomaterials.2013.09.103 PMid:24125774

45. Martin-Sole O, Rodo J, Garcia-Aparicio L, Blanch J, Cusi V, Albert A. Effects of plateletrich plasma (PRP) on a model of renal ischemia-reperfusion in rats. PLoS One. 2016 Aug 23;11(8): e0160703. DOI: https://doi.org/10.1371/journal.pone.0160703 PMid: 27551718 PMCid: PMC4994962