The role of Platelet-Rich Plasma (PRP) in burn wound healing: a literature-review

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ABSTRACT
Burn-related morbidity and mortality are usually caused by secondary infection and long healing time. In these circumstances, the use of products that can accelerate and enhance the wound healing process is urgently needed. One breakthrough in wound healing therapy is platelet-rich plasma (PRP). Platelet-rich plasma is autologous plasma with a platelet concentration above the normal value. This study is a literature review aiming to describe the role of PRP in burn wound healing. PRP has various mechanisms in burn wound healing, such as increasing hemostasis, releasing growth factors, reepithelialization, inducing fibroblast proliferation in the extracellular matrix, and promoting angiogenesis which increases the rate of wound healing. In addition, it also has an antimicrobials effect. Previous studies have been done in animal models and humans to prove the efficacy of PRP in burn wound healing. Most studies have revealed that PRP can accelerate wound healing time and increase the quality of wound healing. So, using PRP in burns can be very useful for patients to reduce burn morbidity and mortality.

Keywords: Platelet-Rich Plasma, Burn Wound, Healing, Literature Review.


INTRODUCTION
Burn wounds are skin tissue damage caused by contact with sources of heat, cold, electricity, radiation, or chemicals. Burn wounds can penetrate muscle and bone. The incidence of burns reaches 6 million annually with a mortality rate of 6-7%.1 Death from burns reaches 180,000 people globally, and the majority occur in low-middle income countries. Burns can cause death and disability, with long healing times and high health care costs. Burn-related morbidity and mortality are usually caused by secondary infection and long healing time.2

Debridement and skin grafting are promising methods, but often the donor skin graft area is insufficient, or the patient’s condition is unsuitable for surgery, impeding the skin graft.3 In these circumstances, products that can enhance the wound healing process are urgently needed. Various new dressings and pharmacotherapy for burns have been developed, one of which is platelet-rich plasma.4

Platelet-rich plasma is autologous blood plasma enriched with platelets to have a platelet concentration above the normal value. Platelet-rich plasma is produced from centrifuged blood and combined with thrombin and calcium chloride as a thick coagulum gel.5 Platelets are important in wound healing because they will migrate to the wound site and coagulate. Activated platelets are also a rich source of growth factors and cytokines. Research shows that growth factors can mediate wound healing.6 Certain growth factors, such as platelet-derived endothelial cell growth factor (PDGF) and Insulin-Like Growth Factor-I (IGF-I), work by inhibiting the apoptotic pathway in facilitating various stages of wound healing.3 The role of PRP in wound healing have been known, but its role in burn wound has not been widely discussed. Understanding PRP is very important to reducing burn morbidity. This study will review the role of PRP in burn wound healing.

METHODS
This study is a literature review investigating the role of PRP in burn wound healing. We performed an extensive search in Pubmed Database on 10th May 2022 with keywords “PRP”, “burn”, and “wound healing”. Articles in English and Indonesian languages were included. The eligible literature was collected from different kinds of studies through the 2010-2021 period. A not full-text article, limited access to the supplementary data, and articles which not include the role of PRP in wound healing were excluded in this study. The literature bias was evaluated by JBI Critical Appraisal checklist by authors independently.

RESULTS
Definition of Platelet-Rich Plasma
Platelet-rich plasma is autologous plasma with a platelet concentration above the normal value. Platelet-Rich Plasma can be defined as blood plasma containing 1,000,000 platelets/µl with a plasma volume of 5 mL.7 Blood consists of 55-60% plasma, and the rest is a component of blood cells in the form of red blood cells, white blood cells, and platelets. Blood plasma is a yellowish liquid composed of 90 percent water and 8 percent protein (albumin, globulin, and clotting factors such as fibrinogen and prothrombin). The function of plasma is to transport other substances. Normal plasma volume in the...
human body is estimated at 5% of body weight; roughly in a 70 kg male, body plasma volume is around 3500 mL. The meaning of autologous is derived from the organism itself or taken from human blood itself. The concentrations of cells in PRP are as follows: 94% platelets, 1% red blood cells and 1% white blood cells.\(^8\)

**Preparation of Platelet-Rich Plasma**

The most common method of PRP preparation begins with taking a whole blood sample by venipuncture into a citric acid dextrose (ACD) tube. Thirty milliliters of blood will produce about 3-5 mL of PRP. The blood is then centrifuged until separated into 3 layers: plasma, buffy coat, and red blood cells (RBC). Plasma has a platelet concentration gradient with platelet-poor above and platelet-rich (PRP) near the buffy coat. The plasma layer and buffy coat were transferred into a new tube without anticoagulant and re-centrifuged. The upper two-thirds of the platelet-poor plasma (PPP) is removed. The lower third, rich in platelets (PRP) with little red cell contamination, was tested for virology and frozen for subsequent application. In the second generation PRP preparation with a faster process, blood is collected in a tube without anticoagulant and centrifuged immediately in a time equal to or less than 2 minutes. A fibrin matrix containing leukocytes and platelets was then isolated.\(^9\)

**Mechanism of PRP in Wound Healing**

The wound healing process in tissue involves various components; one of them is the growth factor (GF). GF consists of epidermal growth factor, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor, and others. PDGF and TGF-β1 are two major modulators in wound healing. PDGF has activity during the early phase of wound healing. In addition, PDGF can increase dermal regeneration, collagen and protein synthesis for migration processes, angiogenesis, and TGF-β expression. Transforming growth factor-beta is said to be an important mediator during tissue repair.\(^10\)

Besides growth factors and extracellular matrix, platelets are one of the components in the wound healing process. Platelets are the first cells to appear at the time of injury and are activated in the early inflammatory phase of the wound healing process. Platelets have a role in homeostasis, occurring during the stages of attachment, aggregation, clot formation, and the release of substances that promote tissue repair. This process affects the reactivity of blood vessels involved in angiogenesis and inflammation. Platelets are also a natural reservoir for various types of GF.\(^11\)

Platelet-rich plasma (PRP) is a simple, efficient and minimally invasive treatment method. PRP consists of centrifugation of autologous blood followed by separating and extracting plasma and buffy coats to achieve high platelet concentrations. The platelet content of PRP is 3 times higher than the normal value in the blood. PRP has been used in several medical treatments, including dentistry, dermatology, plastic surgery and maxillofacial surgery, acute trauma, and veterinary medicine. PRP has been reported to have beneficial effects on wound healing in various areas of surgery and the treatment of acute, chronic, and diabetic wounds.\(^12\)

The rationale for the widespread use of PRP is that platelets facilitate access to critical GFs and various signaling molecules (leukocyte-derived catabolic cytokines and fibrinogen) that regulate tissue healing processes. In addition, high platelet concentrations will result in increased release of various bioactive factors, which will ultimately enhance the healing process. The use of PRP is considered safe due to its autologous nature and minimal complications in long-term use (Figure 1).\(^11\)

**The Role of PRP in Burn Wound Healing**

The use of PRP has shown benefits in the treatment of burns. Platelets in PRP will release active mediators within 10 minutes of clot formation. PRP is stable and does not lose effectiveness within 8 hours of PRP preparation.\(^13\) PRP mechanisms in burns are: (1) increasing hemostasis, thereby reducing blood loss; (2) release of growth factors, reepithelialization, fibroblast proliferation, and angiogenesis, thereby increasing the rate of wound healing; (3) antimicrobials, thereby reducing the risk of infection.\(^8,14\)

PDGF and TGF beta components are important growth factors in PRP, especially in the tissue healing process. A study by Kim et al. found that burn patients treated with topical PRP had 80-100% epithelization in 4 to 20 days. The same study also investigated the topical application of PRP 0.5% enhances the reepithelialization process by upregulating cell cycle regulatory proteins such as cyclin A and CDK4 in HaCaT keratinocyte cells.\(^10\)

A study by Shin et al. revealed that PRP increases fibroblast proliferation by upregulating the expression of MMP-1 and type I collagen in human dermal fibroblasts. Fibroblasts are the most significant cells in the extracellular matrix (ECM) synthesis and remodeling. PRP is a potent matrix metalloproteinase (MMP)-1 stimulator reorganizing the extracellular matrix during the wound healing phase.\(^15\)

Klosova et al. investigated the effect of PRP on the scarring process following deep burn surgery in 23 patients with 38 scars.
The study showed that the combination of split-thickness skin grafting (STSG) with PRP showed a reduced scar time and better results in tissue healing through increased reepithelialization and angiogenesis. A study on burns with 34% TBSA showed an increase in hemostasis from using PRP compared to platelet-poor plasma. The hemostatic qualities of PRP can reduce blood loss, thereby providing a well-vascularized bed in the skin graft. PRP also contributes to accelerated healing time, increased vascular growth, fibroblast proliferation, and reepithelialization.

The application of PRP on burns shows antimicrobial capabilities by reducing and preventing bacterial invasion, thereby reducing the occurrence of infection. In old age, with a decrease in growth factors such as epidermal cells, there will be a decrease in the ability to increase tissue healing. Giving PRP in old age can still improve wound healing. PRP can also accelerate the repair of the extracellular matrix. PRP can be administered as a topical preparation, added to graft, and injected directly at the wound site.

In the porcine model with full-thickness burns, treatment with PRP gel showed a significant increase in vascular growth and fibroblast proliferation. Another study in a mouse model showed that PRP injection in the burn scar area significantly reduced allograft in burn neuropathic pain 4 weeks after treatment. A study in a canine model revealed that 45% full thickness burns healed completely by administration of autologous PRP injection through microneedles on day 28.

However, there is also an animal model study with different results regarding the effect of PRP in burn wounds. In a porcine model with partial-thickness burn by Singer et al., topical autologous PRP and standard topical antibiotics produce equal rates of reepithelialization and scar depth.

In addition to animal models, PRP has been investigated in human clinical trials. A meta-analysis of 8 RCT studies stated that treatment with PRP in burns could improve wound healing (OR 4.43, 95%CI 1.3-9.22), decrease wound healing time (OR 4.23, 95%CI 1.48 to 2.98), and reduce the incidence of side effects (OR 0.30, 95%CI 0.11-0.78) such as neuropathic pain and scarring. This result was confirmed by another meta-analysis study, which stated that PRP increased burn healing rate, decreased burn healing time, and reduced scar.

In addition to healing wounds and reducing the risk of infection, PRP has also been found to reduce scar tissue. Treatment of patients with post-burn scars with intrasplenal PRP injection was better than silicone-based products. A meta-analysis of the long-term impact of PRP on post-burn scars is still being conducted.

CONCLUSION
Previous studies, especially randomized controlled trials, have stated that PRP is an excellent modality for use in burns. Currently, PRP is available in Indonesia and is often used in beauty clinics for cosmetic purposes. The use of PRP in burns can be very useful for patients to reduce burn morbidity and mortality.

CONFLICT OF INTEREST
There is no competing interest regarding the manuscript.

ETHICS CONSIDERATION
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AUTHOR CONTRIBUTIONS
All authors equally contribute to the study from the conceptual framework, data acquisition, and data analysis until reporting the study results through publication.

REFERENCES
