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Effect of Topical Platelet-Rich Plasma on Burn Healing After Partial-Thickness Burn Injury

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Background: To investigate the effects of platelet-rich plasma on tissue maturation and burn healing in an experimental partial-thickness burn injury model.

Material/Methods: Thirty Wistar albino rats were divided into 3 groups of 10 rats each. Group 1 (platelet-rich plasma group) was exposed to burn injury and topical platelet-rich plasma was applied. Group 2 (control group) was exposed to burn injury only. Group 3 (blood donor group) was used as blood donors for platelet-rich plasma. The rats were killed on the seventh day after burn injury. Tissue hydroxyproline levels were measured and histopathologic changes were examined.

Results: Hydroxyproline levels were significantly higher in the platelet-rich plasma group than in the control group (P=.03). Histopathologically, there was significantly less inflammatory cell infiltration (P=.005) and there were no statistically significant differences between groups in fibroblast development, collagen production, vessel proliferations, or epithelization.

Conclusions: Platelet-rich plasma seems to partially improve burn healing in this experimental burn injury model. As an initial conclusion, it appears that platelet-rich plasma can be used in humans, although further studies should be performed with this type of treatment.

MeSH Keywords: Burns • Models, Animal • Platelet-Rich Plasma • Wound Healing

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Background

Burn injury is a major cause of trauma to the human body, causing death and disability, with a long healing period and high health care costs. The mortality rate of burn injury is decreasing with new treatment modalities, although secondary infections and long healing periods still affect mortality rates. Early debridement and skin grafting are successful, but insufficient graft donor area and unsuitable patient circumstances for surgery hinder skin grafting. In these circumstances, using products that increase the wound-healing process often affect patient morbidity and mortality. For this purpose, different kinds of dressings and pharmacotherapies have been developed, but most of them are costly, and the mechanisms underlying these therapies have not been fully documented.

Growth factors have been implicated in mediating the normal healing process as well as playing a role in impaired wound healing. Certain growth factors, such as platelet-derived endothelial cell growth factor (PDGF) and insulin-like growth factor-I (IGF-I), inhibit the apoptosis pathways necessary for the rapid turnover of cells required to facilitate the different stages of physiologic wound healing. The wound healing effects of growth hormone (GH) appear to be directly and indirectly associated with IGF-1 expression. Poffenbarger and Haberal reported that a glycoprotein named nonsuppressible insulin-like activity (NSILA) exhibits insulin-like activity on fibroblasts in tissue and modulates the fibroblastic response in wound healing [1].

Platelet-rich plasma (PRP) is a new adjunct that is increasingly used to treat soft and bony tissue defects to accelerate bone formation, especially in oral and maxillofacial bone reconstructive surgery, and in managing chronic nonhealing wounds [2–5]. Platelet-rich plasma is produced from centrifuged blood combined with thrombin and calcium chloride as a viscous coagulum gel, which is a rich source of growth factors released by activated platelets [3,4,6].

Platelets are important in the wound healing process. They move immediately to the wound site and begin coagulation. Platelets are a rich source of wound-healing growth factors and cytokines. They release multiple growth factors and cytokines, including transforming growth factor-β (TGF-β1 and β2), transforming growth factor-α (TGF-α), vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PDGF), epidermal growth factor (EGF), platelet thromboplastin, thrombospondin, coagulation factors, fibroblast growth factor (FGF), platelet activating growth factor-4, calcium, serotonin, histamine, and hydrolytic enzymes with degranulation triggered by proteins such as thrombin [3,4,6]. It has been demonstrated that platelet-derived growth factors are successful in treating nonhealing cutaneous human wounds [7].

Growth factors are essential for cellular activities involved in wound repair. Growth factors attract cells to the wound site; they stimulate cell proliferation and increase differentiation and extracellular matrix deposition [8]. Transforming growth factor-β is important in tissue repair, and it was demonstrated that TGF-β has therapeutic value in the treatment of chronic, nonhealing wounds [7]. Platelet-derived endothelial cell growth factor improves dermal regeneration, promotes protein and collagen synthesis causing endothelial migration or angiogenesis, and increases expression of TGF-β [7]. Transforming growth factor-β and PDGF levels are higher in platelet-rich plasma compared with platelet-poor plasma (PPP) [7]. Using the effects of TGF-β on wound healing (e.g., promoting differentiation and proliferation), we aimed to achieve enhanced wound healing and more-organized collagen in burn wounds treated with PRP gel compared to controls, without excessive deposition of connective tissue or scar formation.

Although the positive effects of PRP on graft maturation and wound healing are well known, a similar effect on burn healing is not clear. This study sought to investigate the effects of PRP on burn wound healing in an experimental partial-thickness hot water burn injury.

Material and Methods

This study was performed at the Experimental Research Center of Baskent University with the permission of the Experimental Research Ethical Committee of Baskent University Faculty of Medicine. Thirty male Wistar albino rats weighing 250–300 grams were used. All rats were brought to the Experimental Research Center 1 week before the experiment and kept in special cages under controlled temperature (22C), humidity, and lighting conditions (12-hour day, 12-hour night). All rats received standard rat chow and water.

Rats were randomly and equally divided among 3 groups. Each group consisted of 10 rats. Group 1 rats (study group; n=10) were exposed to PRP application after burn injury; group 2 rats (control group; n=10) were exposed to burn injury only; and group 3 rats (blood donor group; n=10) were used as blood donors for the preparation of PRP.

Experimental design

All animals were anesthetized by an intraperitoneal injection of 50 mg/kg ketamine hydrochloride and 10 mg/kg xylazine hydrochloride. Under sterile conditions, a 3×3×3 cm^3 sponge (Vileda, Procter & Gamble Company, Cincinnati, OH) was kept in boiling water and touched to the rats shaved dorsum for 35 seconds with its own weight to induce a partial-thickness burn injury. The 35-second duration was based on

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results of a preliminary study. Partial-thickness burn injury was confirmed with histopathologic analyses. In group 1, the burn site was covered with OpSite drape (Smith & Nephew, Inc., Wound Management, St. Petersburg, FL) after the application of topical PRP. In group 2, the burn site was covered with OpSite drape after the application of saline. After experimentation, all rats were kept in special cages under controlled temperature, humidity, and lighting conditions. All rats were fed with standard rat chow and water. Rats were given 0.002 µg/kg fentanyl citrate twice a day for postoperative analgesia. All rats were killed after administration of anesthesia (60 mg/kg intraperitoneal ketamine) on the seventh day after burn injury.

Preparation of platelet-rich plasma

Platelet-rich plasma was derived after 2-step centrifugation of blood taken from the rats in group 3. With the first soft, short spin (1500 rpm, 20°C, 10 minutes), the plasma fraction was separated from the red blood cells. Then, the plasma fraction was separated with a hard, long spin (2000 rpm, 20°C, 15 minutes) into the PRP and the plasma-poor platelets. After this, the PRP was combined with thrombin (Diathrombin, Diamed, Switzerland) and calcium chloride (Calcium Chloride, Diamed, Switzerland, 0.02 mol/L) to activate platelets to produce sufficient clot formation that could be applied on the burn site. The mixture ratio was 1 mL: 0.1 mL: 1 mL (PRP-Thrombin-Ca Chloride).

Measurements

After the rats were killed on the seventh day, the burn site was excised and tissue samples were sent to the Biochemistry Department for detection of tissue hydroxyproline levels and to the Pathology Department for histopathologic examinations.

Tissue hydroxyproline levels were measured by using Reddy and Enwemeka's method [9]. Tissue specimens were preserved at –86°C. Hydroxyproline measurements were performed by spectrophotometer at 563 nm.

A single pathologist who was included in the study and blinded to all information regarding the groups performed the histopathologic examination of the tissues. Tissue specimens were fixed in a 10% formaldehyde solution, and then embedded in paraffin. Histopathologic examinations for wound healing were assessed by light microscope with hematoxylin-eosin staining, and collagen deposition was assessed by light microscopy with trichrome staining in ×100 and ×200 magnification areas.

The wound healing process was assessed with a modified Ehrlich-Hunt numeric scale for polymorphonuclear leucocytes (PMNL), fibroblasts, vessel proliferation, and collagen deposition as follows: 0 (none), 1 (focal), 2 (mild), 3 (moderate), and 4 (significant). Epithelization was assessed as present or absent.

Statistical analyses

All data are expressed as mean ±SEM. Nonparametric data were compared using the chi-square test. The others were compared using the *t* test. Values for *P* less than 0.05 were accepted as significant.

Results

Two rats from each group died during the experiment, so the statistical analysis was performed with 8 rats in each group.

Hydroxyproline levels

In the study group, mean tissue hydroxyproline (hyp) level was detected as 0.95±0.35 µg hyp/g, whereas in the control group mean tissue hyp level was detected as 0.69±0.08 µg hyp/g. The hyp levels were significantly higher in the study group than in the control group (*P*=.03) (Figure 1).

Histopathologic examination

In both groups, partial-thickness burn injury was confirmed with macroscopic and microscopic examination. Statistically, except for the inflammatory cell (PMNL) infiltration, there was no significant difference between the groups (Figure 2).

Inflammatory cell (polymorphonuclear leucocytes) infiltration

In the study group, the mean PMNL score was 1±0.53, whereas in the control group it was 2.375±0.51 (mean ±SEM). Therefore, inflammatory cell infiltration was statistically higher in the control group (*P*=.005). Moderate inflammatory cell infiltration from the control group and mild inflammatory cell infiltration from the study group are shown in Figures 3 and 4.

Fibroblast infiltration

In the study group, the mean fibroblast score was 0.625±0.51, whereas in the control group it was 0.375±0.51 (mean ±SEM). Although the fibroblast score was higher in the study group, there was no significant difference between the groups (*P*=.31). Focal fibroblast infiltration from the study group is shown in Figure 5.

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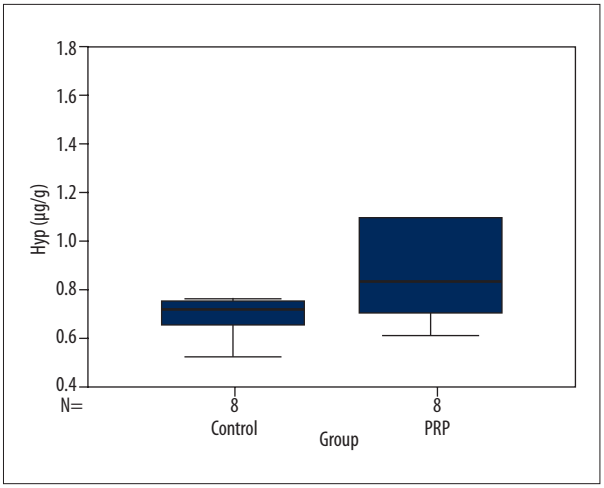

Figure 1. Tissue hydroxyproline levels of the groups.

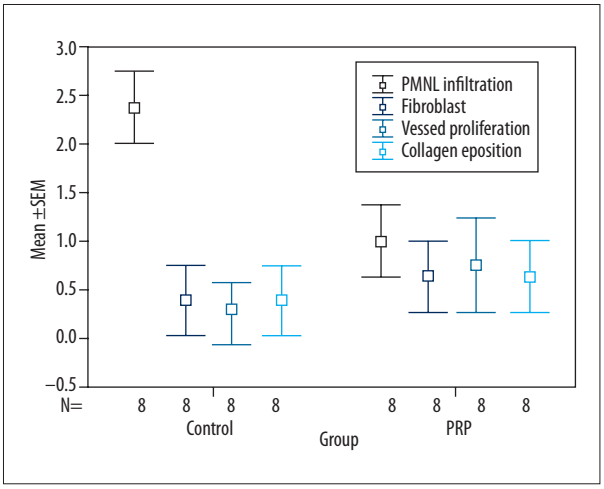

Figure 2. Distribution of polymorphonuclear leucocytes infiltration, fibroblasts, vessel proliferation, and collagen deposit in both groups.

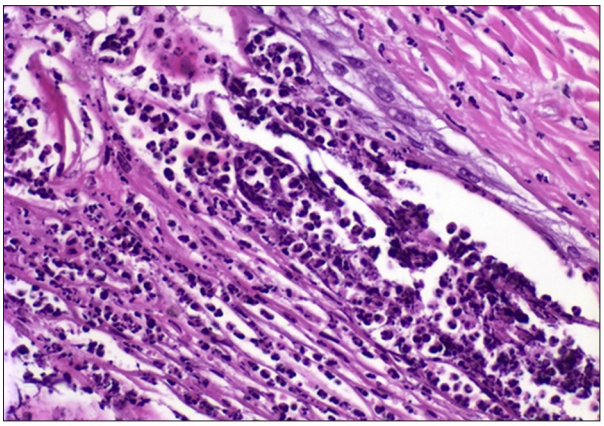

Figure 3. Moderate inflammatory cell infiltration in the control group (H-E ×40, group 2).

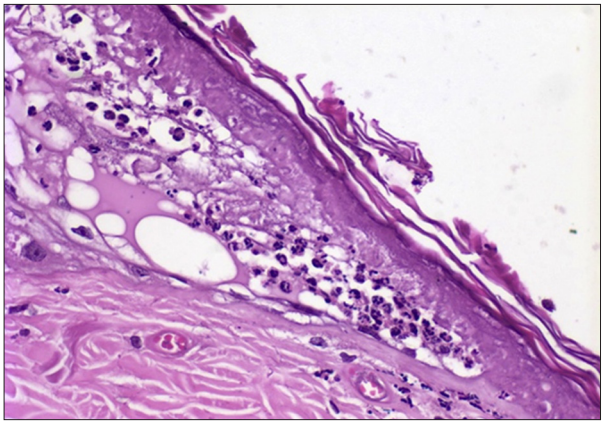

Figure 4. Mild PMNL infiltration in the study group (H-E ×40, group 1).

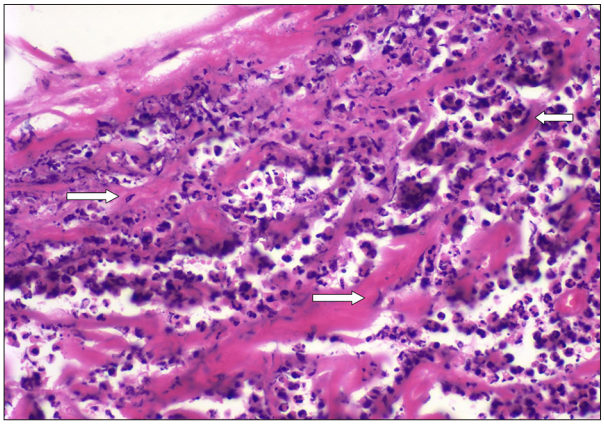

Figure 5. Focal fibroblast infiltration in the study group (H-E ×40, group 1).

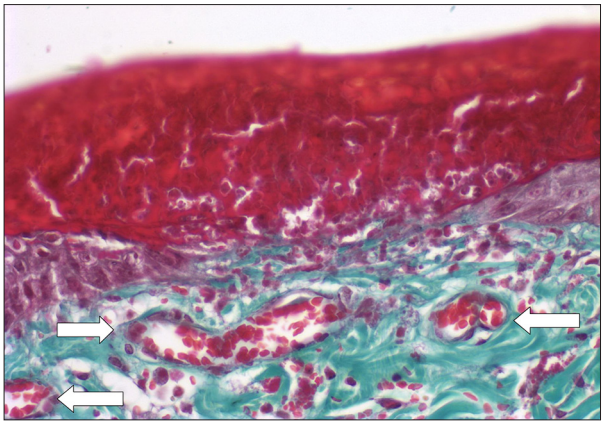

Figure 6. Mild vessel proliferation in the study group (Masson trichrome ×40, group 1).

Vessel proliferation

In the study group the mean vessel proliferation score was 0.75±0.7, whereas in the control group it was 0.25±0.46 (mean ±SEM). Vessel proliferation score was higher in the study group;

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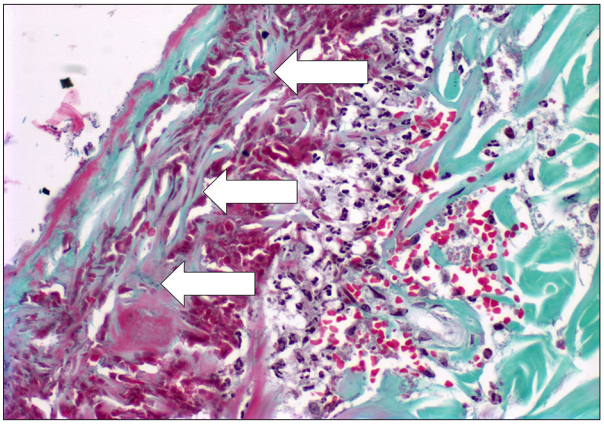

Figure 7. Mild collagen deposition in the study group (Masson trichrome ×40, group 1).

however, no significant difference was detected between the groups (*P*=.26). Mild vessel proliferation from the study group is shown in Figure 6.

Collagen deposition

In the study group, the mean collagen deposition score was 0.625±0.51, while in the control group it was 0.375±0.51 (mean ±SEM). Collagen deposition scores were higher in the study group but no significant difference was detected between the groups (*P*=.31). Mild collagen deposition from the study group is shown in Figure 7.

Epithelization

In the study group the epithelization rate was 37.5%, while in the control group it was 25%. The epithelization rates were higher in the study group, but there was no significant difference between the groups (*P*>.05).

Discussion

Patient age, burn depth, and size of burn area are the most-important factors that influence mortality and morbidity after thermal injuries. Burn depth is also the most important factor affecting patients' long-term appearance and functioning [10]. Malnutrition, immunosuppression, and extensive burn area provide a suitable environment for microorganisms; such infections are the most important cause of mortality and morbidity. In laboratory studies it has been shown that topical administration of bone marrow cells increases dermal fibroblast population, vessel proliferation, and wound healing [11,12].

Burn treatment in patients who have an extensive burn area is difficult. Lack of autografts is an important obstacle for early debridement and grafting [13]. For this reason, wound covering materials and artificial skin substitutes were developed and are used, but their indications are not yet clear. The first laboratory products used for this purpose were epithelial cells produced in a laboratory environment, but approximately 3 weeks are needed to produce the few thousand cm^2 area required in extensive burns [13]. Desired properties of wound cover materials include forming a barrier against fluid loss and microorganisms, supporting increasing cells in wound healing, and allowing vessel proliferation, keratinocyte adhesion, and differentiation; unfortunately, no such material currently exists.

Platelet-rich plasma contains a high level of platelets, clotting factors, cytokines, and growth factors. They start releasing these activated factors 10 minutes after clotting, and more than 95% of growth factors are released in the first hour [3,4]. Platelet-rich plasma is stable for approximately 8 hours after preparation [3,4]. The most important growth factors in PRP are TGF-β and PDGF. They affect every step of wound healing by triggering cell growth and differentiation. Several *in vivo* and *in vitro* studies showed that all cells in the wound healing process are sensitive to the growth factors [5]. Fibroblasts are sensitive to bFGF, PDGFa, PDGFb, IGF, and EGF [14]. Epidermal growth factor is a chemotactic factor for fibroblasts, and topical application of EGF increases epidermal regeneration and strength of wound tension [5]. Endothelial cells are sensitive to bFGF and VEGF [15]. Vessel proliferation is triggered by VEGF, PDGF, and bFGF [16]. Platelet-derived endothelial cell growth factor stimulates fibroblast and smooth muscle cell migration and proliferation, increases collagen deposition, and is also a chemotactic factor for neutrophils and monocytes [6]. Furthermore, it has been shown that chondrocyte, osteoblast, and periosteal cell proliferation is promoted by PDGF and bFGF [17]. Transforming growth factor-β1 regulates cell differentiation, proliferation, chemotaxis, and synthesis of several extracellular matrix proteins [6]. In animal models, it has been shown that topical application of TGF-β1 increases collagen synthesis, granulation tissue, and strength of wound tension [5,18]. There is 4 times more TGF-β in PRP than in PPP [6]. Furthermore, TGF-β increases suprabasal cell proliferation and epidermal regeneration [6]. Collagen, fibronectin, and glycosaminoglycan synthesis from fibroblasts is stimulated by TGF-β [6]. Transforming growth factor-β triggers collagen synthesis and quickens maturation of collagen in the early period of wound healing [6]. In addition, using TGF-β and PDGF together increases collagen deposition more than using TGF-β alone [6].

It has been demonstrated that PRP increases wound healing in acute trauma wounds, chronic nonhealing wounds, and incisional wounds, and is effective in soft and hard tissue reconstructions [2,3,5,6,18–20]. Furthermore, PRP increases epithelial cell differentiation and organization of collagen bunches [6]. Also, PRP enhances tissue incorporation of biological mesh [21]. It has been shown that the inflammatory

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phase is reduced, and prolonged inflammation (which often leads to bacterial infections and scar formation) does not exist in wounds treated with PRP [6]. Hao et al. showed that using PRP with acellular xenogeneic dermal matrix for treatment of deep second-degree burns decreased infection rate and increased wound healing [22].

The literature on use of PRP in burns is sparse. Separate growth factors have shown beneficial results in the treatment of burns [23]. Furthermore, an animal study and several case reports showed improved burn wound-healing time after the application of PRP [23]. A deep dermal burn could benefit from PRP through its hemostatic antimicrobial abilities and the positive effects seen in wound healing [23]. A recent review showed a significant benefit of platelet-rich plasma on wound healing in acute wounds and it improved long-term outcome of laser therapies [24].

There are several studies suggesting that addition of PRP to the graft site enhances wound healing, promoting epithelization and angiogenesis in split-thickness skin grafts and donor sites [25,26]. Klosová et al. demonstrated that the viscoelastic properties of scars treated with the combination of split-thickness skin grafting (STSG) plus autologous platelet concentrate return more rapidly to the plateau state than areas treated with STSG only [27].

In a recent study, PRP increased the speed of repair of the extracellular matrix and its components in deep second-degree burn wounds in horses, and treatment with 2 applications of PRP accelerated formation of extracellular matrix during the first half of wound healing [28].

We have shown that in the study group, PMNL infiltration was significantly lower than in the control group, whereas there were no statistically significant differences between groups in terms of fibroblast infiltration, vessel proliferation, collagen deposition, or epithelization.

The difference between the wound healing processes in the burn wounds versus regular burn wound healing may be the cause of this result. As opposed to regular wound healing, in burn wounds there is no vessel rupture and no hemorrhage into the wounded area. This hemorrhagic infill constructs a skeleton structure for cells coming into the wound site, including neutrophils, monocytes, fibroblasts, and endothelial cells. Moreover, in burn wounds, blood supply is reduced because of the damaged vessels. At the burn site it is hard to define healed parts because of this lack of hemorrhage, which determines the borders of the wound. Although in partial-thickness burn injuries cellular damage generally exists in the upper dermis, in the lower dermis the structural matrix damage is minimal [29]. Thus, structural matrix replacement is limited, and wound healing in partial-thickness wounds usually does not involve replacement of damaged structural matrix [30].

Further evidence supporting our conclusion is the statistically higher tissue hydroxyproline levels in the PRP-treated group, which is an important indicator in wound healing. In the vertebrata, nearly all the hydroxyproline is present in collagen; therefore, determining the hydroxyproline level is an adequate method for assessing collagen metabolism.

Conclusions

Hydroxyproline levels were statistically higher in the PRP group than in the control group (P=.03). Histopathologically, there was significantly less inflammatory cell infiltration (P=.005) and there were no statistically significant differences between groups in fibroblast development, collagen production, vessel proliferations, or epithelization. Platelet-rich plasma seems to partially improve burn wound healing in this experimental burn injury model.

Use of platelet-rich plasma can be an option for patients who have extensive burn areas with no chance for grafting to accelerate the burn healing process. More detailed studies are required to bring this treatment into clinical use.

Declaration of interest

The authors report no conflicts of interest.

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