Effectiveness of topical administration of platelet-rich plasma on the healing of methicillin-resistant *Staphylococcus aureus*-infected full-thickness wound model

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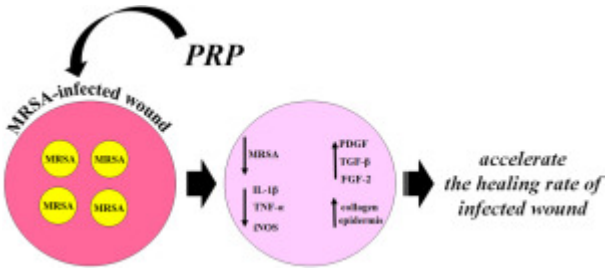
Summary

This study aimed to investigate the wound-healing activity of animal platelet-rich plasma (PRP) in wounds infected with methicillin-resistant *Staphylococcus aureus* (MRSA) in rats. After wound induction, the rats were divided into three groups: noninfected animals treated with PRP (PRP group), MRSA-infected animals treated with mupirocin (standard control group), and MRSA-infected animals treated with PRP (MRSA+PRP group). Scratch assays, MTT test, and live/dead cells were also investigated. Total bacterial count, parameters of wound area, histopathological assessment, and expressions of IL-1β, TNF-α, iNOS, PDGF, FGF-2, and TGF-β mRNA levels and immunofluorescent staining of CD31 and collagen type 1 were assessed. The results showed that culture with PRP increased migration. PRP only showed cytotoxicity in a concentration of 100%. Topical application of PRP (50 μL) reduced the wound area and total bacterial count compared with the control group ($P<0.05$). The mRNA levels of IL-1β, TNF-α, and iNOS expression on days 7 and 14 ($P<0.05$) decreased in the treated groups compared with control rats. The mRNA levels of PDGF and TGF-β expression ($P<0.05$) increased in the treatment groups compared with control rats on days 3 and 7 ($P<0.05$). FGF-2 expression was significantly higher in the treated groups compared with the control group on days 7 and 14 ($P<0.05$). Moreover, positive expressions of macrophage colony-stimulating factor (M-CSF), CD31, collagen type 1 and cytokeratin proteins keratinocyte proliferation, and re-epithelization were significantly ($P<0.05$) increased in both PRP and MRSA+PRP-treated groups compared with the control groups on days 7 and 14. Topical administration of PRP accelerated the wound healing in MRSA-infected wound by decreasing the inflammation and improving the proliferative phase.

Graphical abstract



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Introduction

In the wound-healing process, the inflammatory phase is essential for preventing inflammation and tissue regeneration.[1] Inflammatory chemokines activate inflammatory phase, tumor necrosis factor-α (TNF-α), for instance. TNF-α, as a cytokine, plays an important role in the inflammatory phase. Following wound induction, systemic immune response and inflammation are activated and most of the inflammatory cells, such as macrophages, migrate to the wound site.[2] Macrophages promote transition from inflammatory to proliferative phase during wound healing.[3] Interlukin-1β (IL-1β) mediated autophagy in neutrophils.2, 3, 4 Inducible nitric oxide synthase (iNOS) is involved in the wound-healing process by producing NO (nitric oxide).[5,6] Some bacteria infect wound site, increase inflammation, and disturb normal wound-healing process.[7] Previous studies have demonstrated the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA)-related infections as a factor for mortality in the community and in hospitals.[8,9] Despite significant advances in the production of antibiotics and antiseptics, infections resulting from traumatic and surgical wounds still pose a major threat.[10] Antibiotics are typically used for the treatment of infected wounds. The rise in multidrug-resistant bacteria increases the necessity for topical antimicrobial agents that can be used for the treatment of wounds. Some agents have cytotoxic effects on the host organism. Natural and chemical agents are used in wound healing.[10] Platelet-rich plasma (PRP) is autologous plasma that contains more platelets than whole blood that can be used for the treatment of wounds.

PRP is obtained from the whole blood and contains growth and clotting factors and has mitogenic and chemotactic properties.[11] Based on evidence, α-granules released from PRP contain major concentrations of multiple active growth factors, including platelet-derived growth factors (PDGFs), vascular endothelial growth factor (VEGF), and transforming growth factors (TGFs), which promote the wound-healing process through early inflammatory response and granulation tissue formation,[12] keratinocyte proliferation, and re-epithelization during healing process.[13,14] Some studies have also shown the antimicrobial activity of activated platelets in PRP.[15,16] PRP is conventionally used for accelerating wound healing, but its action mechanisms from the point of view of molecular changes in the inflammatory phase are still unknown. In this study, we evaluated the effects of topical administration of PRP on molecular changes of pro-inflammatory factors of IL-1β, iNOS, and TNF-α in wounds infected with MRSA in a rat model.

Section snippets

Animal model

Wistar male rats (170–190 g) were housed individually in steel cages at the Animal Resource Center of Azad University of Urmia with a 12-h light/dark cycle. The animals were fed antibiotic-free food (Javeneh Khorasan Company, Iran) and water *ad libitum*; they were housed and maintained in accordance with the Iranian ethical guidelines for the use of animals. MRSA (ATCC 33,591) purified from clinical samples was prepared at the Pastur Institute (Tehran, Iran).

PRP preparation, activation, and count

The rat PRP was prepared as reported

Effects of PRP on in vitro scratch assay

The results for scratch in Figure 1 show that cells could migrate into cell-free areas from 12 to 48 h. They also show that migration is significantly higher at 48 h, and cells significantly migrate with an increase in time.

Effects of PRP on in vitro cell viability assay

Figure 2 depicts the cell viability for different groups. Cells survived at PRP concentrations of 25% and 50%, whereas they did not survive at a concentration of 100%.

The increase in PRP concentration decreased cell viability; hence, cell viability was zero at a PRP of 100%.

Effects of PRP on live/dead cells

Discussion

Bacterial infection poses a major threat as it prevents wound healing and tissue regeneration through increasing inflammation, scar formation, and pain in wound sites.[7,9,10] The findings showed that the topical administration of the PRP progressively decreased total bacterial count; hence, it had better antibacterial activity than the mupirocin antibiotic. The total bacterial count was less and insignificant in the noninfected PRP because of the open wound during the study. Decreased total

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ethical approval statement