Epidermal Growth Factor (EGF) representing the role of other growth factors contained in Platelet-Rich Plasma (PRP)

by Budi Utomo .

Epidermal Growth Factor (EGF) representing the role of other growth factors contained in Platelet-Rich Plasma (PRP)

Dessyta Sukma Nurmaulinda[1*], Agus Santoso Budi[1], Lobredia Zarasade[1], Budi Utomo[2]

ABSTRACT

Background: Wound care with modern dressings that have been widely used takes time to achieve healing. Therefore, Epidermal Growth Factor (EGF) and Platelet-Rich Plasma (PRP) are developed in wound healing therapy. EGF as the primary growth factor examines whether it is sufficient to represent the role of other growth factors in PRP. EGF is also chosen because of its ease of provision and longer shelf life compared to PRP. This study evaluates the (EGF) representing the role of other growth factors contained in PRP.

Methods: The study was performed on 66 full-thickness wounds in 6 groups of 36 healthy male *Oryctolagus cuniculus* rabbits. Four treatment groups were given EGF and PRP therapies. Two control groups were given no treatment. Half of the groups were evaluated on the fifth day and the rest on the fourteenth day. Assessment on the clinical macroscopic and histopathological numbers of fibroblasts, capillary blood vessels, and type III collagen fibers were stained with Hematoxylin Eosin (HE) and Masson's Trichrome. Data were analyzed using SPSS version 23 for Windows.

Results: There was a statistically significant difference in fibroplasia (p=0.014; p=0.018) on the fifth and fourteenth days. However, there was no significant difference in angiogenesis (p=0.183; p=0.524) or collagenization (p=0.218; p=0.278) on the fifth and fourteenth day. On the fifth day, the number of capillary vessels was highest in the PRP groups (10.60±4.13), and the ratio of type III collagen fibers (53.00±13.00) was the highest in the EGF group. On the fourteenth day, the number of capillaries and the ratio of type III collagen fibers was the highest in the EGF groups (77.00±16.00).

Conclusion: EGF greatly increases the speed of macroscopic healing, accelerates fibroplasia, induces angiogenesis, and is also involved in collagen deposition compared to PRP administration, especially when compared to untreated wounds.

Keywords: Wound, EGF, PRP, Epithelialization, Collagenization.
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INTRODUCTION

A wound is a condition where the tissue is broken due to various things. This condition is immediately followed by a wound healing process, which is very complex.[1,2] The use of Epidermal Growth Factor (EGF) and Platelet-Rich Plasma (PRP) is now being developed in the medical field because wound care with modern dressings that have been widely used takes time to achieve healing.[3,4] EGF can be developed via recombinants and is a product containing a concentration of growth factors. In comparison, PRP is obtained from peripheral blood concentrate. The advantage of EGF and PRP is that they can be produced in large quantities with minimal effort and their characteristics can be maintained so that they can be used for tissue regeneration.[3,4]

EGF is a growth factor that plays a significant role in the process of proliferation, cell differentiation, stimulation of migration, and proliferation of fibroblasts and keratinocytes, encouraging vascular endothelial cell growth and collagen deposition.[5] EGF stimulates keratinocytes, fibroblasts, and endothelial cells in granulation tissue formation. In addition, EGF can stimulate fibroblasts to synthesize Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF). VEGF and HGF are growth factors that play a major role in promoting the angiogenesis process in wounds. Fibroblasts are the primary cells in the dermal layer of the skin that play an important role in the wound healing process and are responsible for various functions such as the secretion of extracellular matrix (ECM) compounds, especially collagen and fibronectin, in addition to remodeling enzymes such as proteases and collagenases. Thus, it is obvious that fibroblasts are the key cells that form the foundation of normal skin.[5-7]

PRP plays a role in wound healing with its high content of exogenous growth factors. PRP can release several growth factors in the form of Epidermal Growth Factor (EGF), Platelet-derived Growth Factor (PDGF), Basic Fibroblast Growth Factor (bFGF), Vascular Endothelial Growth Factor (VEGF),

Insulin-like Growth Factor-1 (IGF-1), and Transforming Growth Factor-β (TGF-β) which is involved in tissue repair and regeneration both in the processes of epithelialization, fibroplasia, angiogenesis, and collagenization.[4,8,9]

EGF and PRP in wound healing therapy are relatively new science used in the medical field, both of which have advantages but have never been compared. As the most important growth factor in this study, EGF will be examined whether it is sufficient to represent the role of other growth factors in PRP. EGF was also chosen because it is easy to provide and can be stored for a long time, compared to PRP, which in its supply must be invasive on the patient and must be used immediately after processing. Based on those mentioned above, this study aims to assess several indicators of wound healing through the macroscopic feature, fibroplasia, angiogenesis, and collagenization on the fifth and fourteenth days according to the phase of wound healing.

METHODS

All animal protocols and experiments were approved by the Animal Care and Use Committee (ACUC) Airlangga University and were performed in accordance with ARRIVE 2.0 guidelines. Peripheral blood was collected from healthy rabbits into vacuum tubes containing sodium citrate anticoagulant. The sample was centrifuged at 4000 rpm for ten minutes at room temperature. The whole blood was divided into three layers; the upper layer was the supernatant, the lower layer was the red blood cells, and the middle layer was the platelet layer. The platelet layer was centrifuged at 2000 rpm for five minutes to give an upper platelet-poor and lower platelet-rich layer. Epidermal Growth Factor (EGF) originated from recombinant *E. coli* and was a product containing growth factors under the brand Easyef[R] produced by Daewong Infion Ltd., Korea.

Thirty-six healthy male *Oryctolagus cuniculus* rabbits were provided by the Experimental Animal Center of Airlangga University, taken at 12 weeks with a weight of 3000 to 3500 grams. Random alloc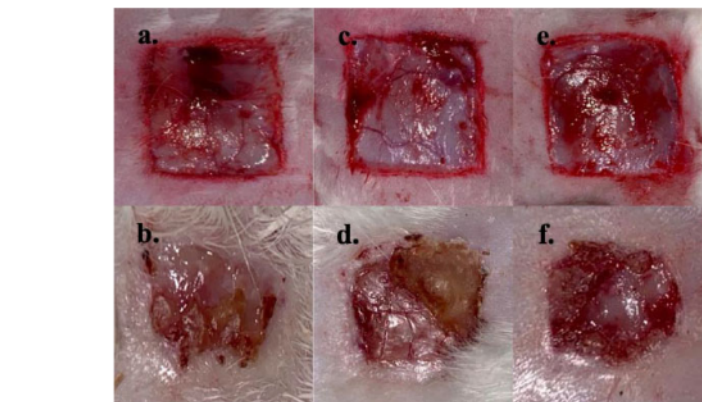ation was carried out by raffling the thirty-six rabbits into six homogeneous groups. The first and fourth groups were given EGF therapy, the second and fifth groups were given PRP therapy, and the third and sixth groups, as the control groups, were not given any treatment. The first, second, and third groups were evaluated on the fifth day. The remaining three groups were assessed on the fourteenth day.

All rabbits in both the treatment and control groups were given an intramuscular injection of penicillin procaine of 100 mg/

Figure 1. Macroscopic view of full-thickness wounds evaluated on day one and day five. (a, b) treatment groups with EGF; (c, d) treatment groups with PRP; and (e, f) control groups without treatment.
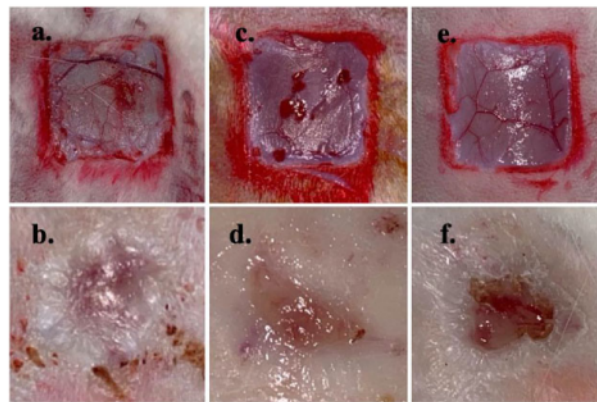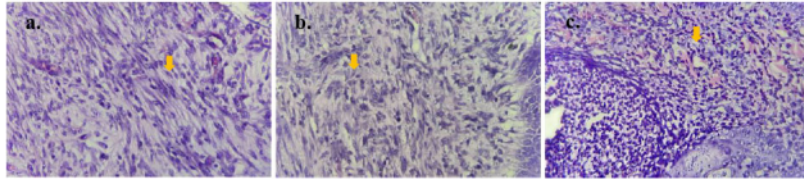

Figure 2. Macroscopic view of full-thickness wounds evaluated on day one and day 14. (a, b) treatment groups with EGF; (c, d) treatment groups with PRP; and (e, f) control groups without treatment.

Table 1. Analysis of fibroplasia by administering EGF and PRP to full-thickness wounds.

Parameters	Day five (Mean±SD)[a]	Day fourteen (Mean±SD)[a]
Epidermal Growth Factor (EGF)	206.33±16.82	194.87±13.89
Platelet Rich Plasma (PRP)	205.33±23.723	159.87±54.06
Control groups	151.00±47.56	103.53±39.78
p-value	0.014*[b]	0.018*[c]

[a] Group statistics analysis. The average value of cells in five randomly high-power fields. Field of view (FOV); [b] ANOVA test (p <0.05); [c] Kruskal-Wallis test (p <0.05); SD: Standard Deviations; *: Statistically significant if p-value less than 0.05.

Figure 3. Histopathological features of fibroplasia were evaluated on day five. (a) EGF treatment groups; (b) PRP treatment groups; and (c) control groups.
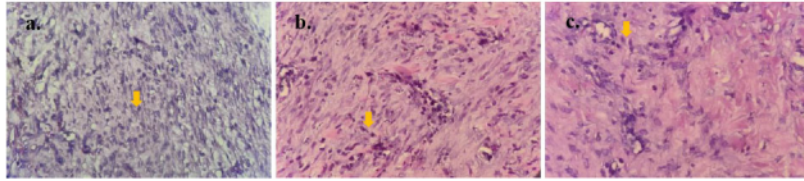

Figure 4. Histopathological features of fibroplasia were evaluated on day 14. (a) EGF treatment groups; (b) PRP treatment groups; c) control groups.

Table 2. Analysis of angiogenesis by administering EGF and PRP to full-thickness wounds.

Parameters	Day five (Mean±SD)[a]	Day fourteen (Mean±SD)[a]
Epidermal Growth Factor (EGF)	8.07±2.41	8.17±2.83
Platelet Rich Plasma (PRP)	10.60±4.13	7.23±1.79
Control groups	7.07±2.91	6.67±2.02
p-value	0.183[b]	0.524[b]

[a]Group statistics analysis. The average value of capillary vessels in five randomly high-power fields. Field of view (FOV); [b]ANOVA test (p >0.05); SD: Standard Deviations; *:Statistically significant if p-value less than 0.05.
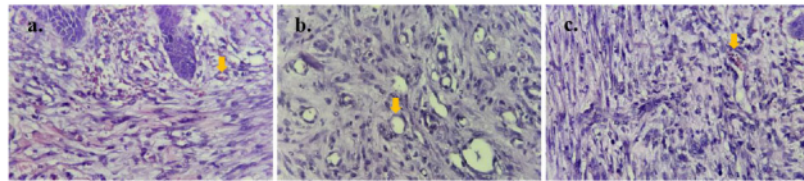

Figure 5. Histopathological features of angiogenesis were evaluated on day five. (a) EGF treatment groups; (b) PRP treatment groups; and (c) control groups.
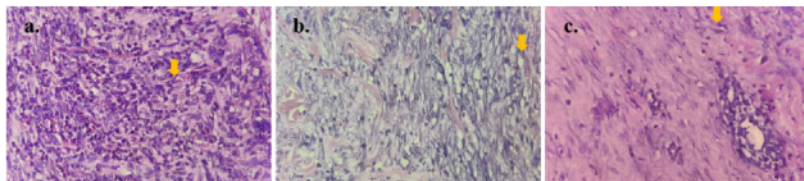

Figure 6. Histopathological features of angiogenesis were evaluated on day 14. (a) EGF treatment groups; (b) PRP treatment groups; and (c) control groups.

kg, then anesthetized with ketamine of 20 mg/kg intramuscularly. The rabbit hair on the back was shaved and disinfected with 10% povidone-iodine, then the surgeries were performed under standard sterile conditions. A full-thickness incision was made onto the rabbits' backs with a 2 x 2 cm size using a hand mesh and surgical blade number 15. Immediately after the skin injuries, each wound surface was treated with 10 ml of EGF for the first and third groups and 100 µl of PRP for the second and fourth groups, while the control groups were not given any treatment. The six wound groups were then covered with transparent dressings (Tegaderm[R], 3 M, St. Paul, MN).

Rabbits were given an injection of 60-100 mg/kg phenobarbital intraperitoneally in the mid-lateral area of the xiphoid process and pubic tubercle. Tissue was taken in the treatment groups and the control groups by taking the skin in full thickness. The collected tissue was stored in filter papers and then put into a 10% Formalin Buffer bottle for fixation.

A tissue incision was done with a thickness of 4-6 µm. According to the manufacturer's instructions, the sections were deparaffinized, rehydrated, graded with ethanol series, and stained with hematoxylin-eosin (HE) and Masson's trichrome stain. The sections were then photographed using a light microscope (Olympus, Japan) with 400 times magnification. Skin sections stained with HE were evaluated to assess the number of fibroblasts and blood vessel capillaries by five randomly collected high-power fields (FOV). The average value of positive cells was calculated using ImageJ software. Sections stained with Masson's trichrome were assessed for the percentage of collagen. An ImageJ algorithm was used to count the number of blue pixels and calculate the total number of pixels per skin section.

The data collected was processed with the help of SPSS version 23 for Windows, then analyzed descriptively in graph tables. Results were reported after conducting Shapiro-Wilk testing for normal distribution. The parametric statistical test was done for the normally distributed data, while non-parametric statistical tests were done for data curves

Table 3. Analysis of collagenization by administering EGF and PRP to full-thickness wounds.

Parameters	Day five (Mean±SD)[a]	Day fourteen (Mean±SD)[a]
Epidermal Growth Factor (EGF)	53.00±13.00	77.00±16.00
Platelet Rich Plasma (PRP)	45.00±1.00	7.00±19.00
Control groups	37.00±19.00	64.00±13.00
p-value	0.218[b]	0.278[c]

[a] Group statistics analysis. The ratio value of fibers to the entire high-power field of view. Percentage (%); [b] ANOVA test (p >0.05); [c] Kruskal-Wallis test (p >0.05); SD: Standard Deviations; *: Statistically significant if p-value less than 0.05.
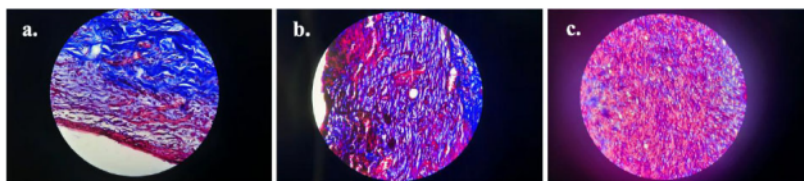
Figure 7. Histopathological features of collagenization were evaluated on day five. (a) EGF treatment groups; (b) PRP treatment groups; and (c) control groups.
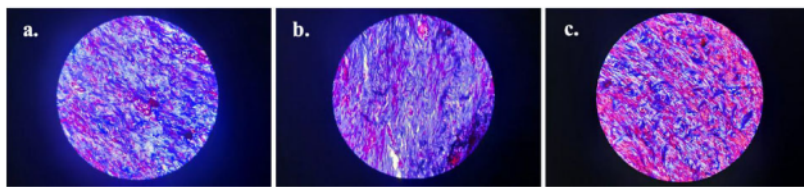
Figure 8. Histopathological features of collagenization were evaluated on day 14. (a) EGF treatment groups; (b) PRP treatment groups; and (c) control groups.

with a slanted distribution. In this study, the comparison tests used were ANOVA and Kruskal-Wallis. A p-value < 0.05 was considered statistically significant.

RESULTS

Based on the analysis of the macroscopic feature of the wounds evaluated on the fifth day, better wound healing was obtained in the EGF and PRP treatment groups compared to the control groups (Figure 1). In the evaluation on the fourteenth day, the best wound healing was found in the treatment groups with EGF, followed by the treatment groups with PRP, and the least in the control groups (Figure 2).

In statistical analysis, p = 0.014 (p <0.05) was obtained on the fifth day with the ANOVA test and p = 0.018 (p <0.05) was received on the fourteenth day with the Kruskal-Wallis test. This means that there were differences in the fibroplasia

on the fifth and fourteenth days with the administration of EGF and PRP in full-thickness wound healing (Table 1).

Group statistics analysis on the fifth day obtained a mean of 206.33 with EGF, 205.33 with PRP, and 151 in the control group. On the fourteenth day, the mean was 194.87 with EGF administration, 159.87 with PRP administration, and 103.53 in the control group. It was concluded that the fibroplasia on the fifth and fourteenth days was best found in the EGF treatment groups, followed by the PRP treatment groups, and the least in the control groups (Table 1).

In the analysis of histopathological picture evaluated on the fifth day, the highest number of fibroblast cells was found in the treatment groups with EGF, the second was found in groups treated with PRP, and the least was in the control groups (Figure 3). On the fourteenth day,

the highest number of fibroblast cells was found in groups treated with EGF, the second highest was in groups treated with PRP, and the least was found in the control groups (Figure 4).

With the ANOVA statistical test, p = 0.183 (p> 0.05) was found on the fifth day and p = 0.524 (p> 0.05) on the fourteenth day. There was no significant difference in the angiogenesis process on the fifth and fourteenth days with the administration of EGF and PRP (Table 2). However, group statistics analysis on the fifth day obtained a mean of 8.07 with EGF administration, 10.6 with PRP, and 7.07 in the control group. On the fourteenth day, the mean was 8.17 with EGF administration, 7.23 with PRP administration, and 6.67 in the control group. It was concluded that the angiogenesis process on the fifth day was best found in the treatment groups with PRP, but on the fourteenth day was best found in the treatment groups with EGF administration, followed by the treatment groups with PRP, and the last was the control groups (Table 2).

Based on the histopathological analysis evaluated on the fifth day, the highest number of capillary vessels was found in the treatment groups with PRP. The second-highest was in groups treated with EGF, and the last was the control groups (Figure 5). On the fourteenth day, the highest number of capillary vessels was found in groups treated with EGF, the second highest was in groups treated with PRP, and the least was in the control groups (Figure 6).

ANOVA statistical test showed p = 0.218 (p> 0.05) on the fifth day and Kruskal-Wallis statistical test showed p = 0.278 (p> 0.05) on the fourteenth day. It was concluded that there was no difference in collagenization on the fifth and fourteenth days with the administration of EGF and PRP (Table 3). On the fifth day of collagenization, a mean of 53% was obtained with EGF, 45% with PRP, and 37% in the control group as a ratio of fibers to the entire high-power field of view. On the fourteenth day of collagenization, a mean of 77% was obtained with EGF, 7% with PRP, and 64% in the control group. Collagenization on days five and fourteen was best found in the EGF group, followed by the PRP group, and finally, the control

groups (Table 3).

In analyzing the histopathological features evaluated on the fifth day, the largest ratio of type III collagen fibers was found in the treatment groups with EGF. The second-highest was in groups treated with PRP, and the last was in the control groups (Figure 7). On the fourteenth day, the largest ratio of type III collagen fibers was found in groups treated with EGF, the second highest was in groups treated with PRP, and the least was in the control groups (Figure 8).

DISCUSSION

EGF and PRP have been reported to improve skin wound healing and began to be used widely in treating wounds. Epithelialization, fibroplasia, angiogenesis, and collagenization are important processes in wound repair.[3,10] However, the systematic comparison of administering EGF and PRP on these factors has not yet been widely discussed.[10-15] We have demonstrated that the positive effects of EGF and PRP on wound healing in a coordinated manner contribute to improved skin wound repair.

One of the first biological effects of EGF noted by Cohen is the hypertrophic development of the skin epidermis with EGF injection. EGF facilitates the regeneration of epidermal cells and plays an important role in the process of dermal wound healing through stimulation of proliferation and migration of keratinocytes.[3,10] On the fifth day of evaluation, there was better wound healing with greater contractility in the EGF and PRP groups. However, on the fourteenth day, it was seen in the EGF groups that the wound had completely closed. In the PRP group, the wound still left some raw surface. In addition, papillary fibroblasts in the basal epidermal layer could help control keratinocyte migration and proliferation with Keratinocyte Growth Factor (KGF).[3,5,6,11-15]

Observations and demonstrations of several previous studies have shown that EGF stimulates the growth of in vitro fibroblast cultures by promoting granulation tissue formation and stimulating fibroblast motility. Administration of exogenous EGF provides faster epithelial regeneration and

less scar contracture in rabbits. Thicker and more cellular epithelium with early fibroblast migration results in less tissue distortion at the macroscopic scale.[3,10] We also found that the highest number of fibroblast cells was found in the EGF treatment groups, the second was found in the PRP group, and the least was in the control group.

EGF can trigger the secretion of growth factors produced by fibroblasts and promote the angiogenesis process, thereby affecting the acceleration of wound healing. Fibroblasts can accelerate the angiogenesis process by releasing pro-angiogenic agents and stimulating endothelial cell production. Fibroblasts are the key cells that form the foundation of normal skin. EGF is able to increase fibroblast proliferation and stimulate fibroblasts to produce Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF), which are essential for the formation of granulation tissue. The fibroblasts in the EGF gel sheet release 3.7 times more VEGF and twenty-five times more HGF.[5,6,11-16] To confirm this, we compared the effect of EGF with PRP. The results showed that on the fifth day, angiogenesis was best seen in the PRP group, but most blood vessel capillaries were seen in the EGF group on the fourteenth day.

Another important stage of wound healing is collagenization. The deposition and arrangement of collagen fibers reduce the possibility of scar repair, which is beneficial to improve the quality of tissue remodeling. Many studies have previously described the primary role of EGF in influencing the migration and proliferation of fibroblasts.[11,12,14] Fibroblasts are the primary cells in the dermal layer of the skin which are also responsible for various functions such as the secretion of Extracellular Matrix (ECM) compounds, mainly collagen and remodeling enzymes such as collagenase.[11,12,14] We also reached the same conclusion in our study. Comparison of type III collagen fibers was greatest in groups treated with EGF therapy, the second was found in groups treated with PRP, and the least was in the control groups both on the fifth and fourteenth days.

CONCLUSION

In summary, we conducted the first comprehensive analysis of the comparative effects of EGF and PRP on wound healing in a baseline experience, which further identified the key roles of EGF and PRP in the three important stages of wound healing. The use of EGF and PRP facilitates various aspects. EGF increases the speed of macroscopic healing, accelerates fibroplasia, induces angiogenesis, and is also involved in collagen deposition better than PRP administration, especially greater when compared to untreated wounds. Although there are still some molecular mechanisms that should be explored in-depth, our research supports the use of EGF as an adjuvant to accelerate wound healing.

CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICS CONSIDERATION

This study was reviewed and approved by The Animal Care and Use Committee (ACUC) Airlangga University with reference number: 2.KE.194.11.2019.

FUNDING

There is no funding to declare.

AUTHOR CONTRIBUTIONS

DSN is responsible for informed consent procedure, improvements and corrections to CRFs, data collection, data monitoring, and implementing research procedures. AS, LZ, and BU are responsible for review and signing of data sources & CRFs.

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