The effects of oral

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The effects of oral antihistamines on the formation of granulation tissue on full-thickness wounds in white rats *Rattus norvegicus*

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ABSTRACT

Background: Granulation tissue is formed during the proliferative phase of wound healing. In the presence of granulation tissue, the process of epithelialization can take place. Disturbance in the formation of granulation tissue, especially hypergranulation, will result in an abnormal wound healing process. Antihistamines have been shown to have an effect on abnormal wound tissue fibroblasts and reduce collagen synthesis both by topical administration in vivo and in vitro culture. This study aimed to investigate the effect of oral antihistamines on granulation tissue formation, collagen deposition, and angiogenesis involved.

Method: The study design used was an experimental randomized post-test only. Thirty-two rats were divided into 2 groups, wherein group 1 was treated as a control while those in the second group were given oral diphenhydramine with a dose according to body weight. Full-thickness wounds were made on the back of all rats. The treatment was carried out every day for 7 days. On the 7th day, granulation tissue specimens were taken with an excisional biopsy from the wound. From each granulation tissue sample, data taken were the granulation tissue thickness, collagen density, and the number of capillaries formed.

Results: Using an independent T-test, the mean thickness of granulation tissue in the treatment group was significantly smaller than the control group (215.82 ± 44.73 µm vs. 304.43 ± 58.61 µm, p<0.005). Mann-Whitney test revealed that the mean number of capillaries in the treatment group was significantly less than the control group (38.11 ± 5.31 vs. 69.66 ± 11.81, p<0.005). Kruskal-Wallis test revealed that the collagen density of the treatment group was significantly smaller than the control group (p<0.0001).

Conclusion: Administration of oral antihistamines can inhibit the formation of granulation tissue in full-thickness wounds and also reduce collagen density and angiogenesis. This can serve as a reference for the effect of oral antihistamines on wound healing, especially in the process of granulation tissue formation.

Keywords: *angiogenesis, antihistamines, collagen, granulation tissue.*
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INTRODUCTION

Wounds are anatomical damage due to trauma or other causes, both physical and chemical, that cause discontinuity of a tissue. Physical trauma that can cause tissue damage includes sharp or blunt trauma, cuts, extreme temperatures, radiation, and blood flow obstruction. Chemicals can cause damage which includes obstruction due to vascular constriction or thrombosis. Dead or damaged tissue will be replaced by new tissue through several processes called the wound healing process. Wounds will be difficult to overcome if there is interference with the healing process.

Closing the wound tissue requires a process of epithelialization. Re-epithelialization of this wound can only occur if the wound has been filled with granulation tissue and becomes parallel to the surrounding skin.[1] Granulation tissue consists of blood clot components, fibroblasts and their progenitor cells that have invaded the area, ECM of new loose and primitive connective tissue produced by wound fibroblasts, new blood vessels, and inflammatory cells.[2]

If there is a problem in the formation of granulation tissue, wound healing will be disrupted.

New approaches to address the problem of normal granulation tissue formation are continuously being developed, including agents that can affect collagen synthesis and the process of granulation tissue formation. From the results of a previous study, it was proven that topical antihistamines could reduce TGF-ß and collagen levels at the end of the proliferative phase or the beginning of the full-thickness wound remodeling phase in experimental animals.[3] However, no studies have analyzed the effects of oral antihistamines on the formation of granulation tissue.

This study aims to investigate the effect of oral antihistamines on the formation of granulation tissue, including collagen density and neovascularization in it. This can be a reference to the effect of

oral antihistamines on wound healing, especially in the process of granulation tissue formation.

METHOD

The study design used was an experimental randomized post-test only. Thirty-two rats (*Rattus Norvegicus*) were divided into 2 groups, wherein group 1 was treated as a control while those in the second group were given oral diphenhydramine. Full-thickness wounds were made on the back of all rats with a dimension of 1.5x1.5 cm, made until the depth of the deep fascia. The wound was closed using a transparent dressing which was fixed with stitches.

In group I, rats were treated as a control without any intervention but were still given 1 cc of distilled water every day by force-feeding. Rats in group 2 are the treatment group. They will be given the diphenhydramine treatment with a dose of 4 mg/kg/day with a dilution of up to 1 ml using distilled water by force-feeding every day until the 7th day.

The treatment was carried out every day for 7 days. On the 7th day, granulation tissue specimens were taken with an excisional biopsy from the wound. From each granulation tissue sample, data taken were the granulation tissue thickness, collagen density, and the extent of angiogenesis represented by the number of capillaries formed.

Granulation tissue thickness was determined by hematoxyline-eosin staining and assessed by an independent reviewer. Thickness measurements were taken from the base of the tissue directly adjacent to the deep fascia to the surface of the outermost layer and were measured in micrometers.

Within the granulation tissue, new capillaries begin to form, which are stimulated by growth factors released by platelets, macrophages, and endothelial cells. The number of endothelial cells within the granulation tissue specimen will be counted in 3 visual fields with Hematoxylin eosin staining. The mean number of capillaries formed in each specimen will be calculated.

The extent of collagen deposition was observed using Masson's trichrome staining. The assessment was carried out using collagen density scoring and expressed on an ordinal scale of 0-4.

RESULTS

The subjects of this study were divided into 2 groups, and each group consisted of 16 experimental animals. The average weight of rats in the treatment group was 224 gr, while in the control group, it was 218 gr. None of the experimental animals died during the research process.

The Thickness of Granulation Tissue

Histopathological pictures of granulation thickness measurements in the control group and the treatment group on the 7th day are shown in Figure 1.

The mean thickness of granulation tissue in group I (control) was 304.43 µm with a standard deviation of ± 58.61 µm, while that in group II (treatment) was 215.82 ± 44.73 µm (Table 1).

The results of the independent T-test showed that the mean granulation tissue thickness in the treatment group was significantly smaller than the control group (p=0.000).

Angiogenesis

Histopathological pictures of the capillaries in the control group and the treatment group on the 7th day are shown in Figure 2.

The mean-rank sum of the mean number of capillaries in the 3 visual fields in group I (control) was 24.5, while in group II (treatment H-7), it was 8.5 (Table 2).

The results of the Mann-Whitney test showed that the mean number of capillaries of the granulation tissue in the treatment group was significantly less than in the control group (p=0.0000).

Collagen deposition

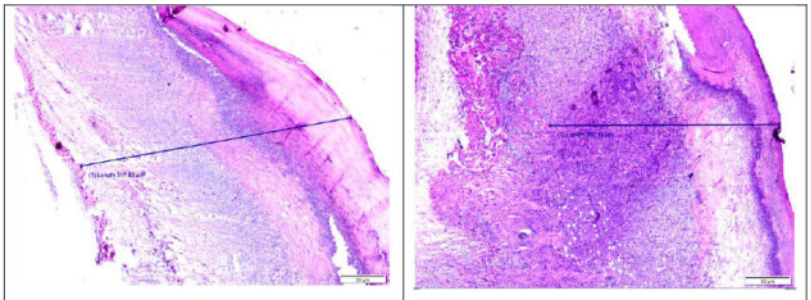
The degree of collagen deposition was examined using Masson's trichrome staining. The histopathological scoring of collagen density (based on observation of 1 visual field with 400x magnification) was assessed by an independent reviewer.

The results of the Kruskal-Wallis non-parametric analysis revealed a score of H (df 1) = 14.49006 (p <0.0001). Therefore, it can be concluded that collagen deposition in the treatment group is significantly smaller than in the control group.

DISCUSSION

The thickness of the granulation tissue in the treatment group was significantly smaller than in the control group. This suggests an inhibition in the process of formation of granulation tissue and its accompanying components, which occurs during the proliferative stage of wound healing.

Granulation tissue formation was observed on day 7. Around the third after injury, macrophages, lymphocyte subsets, and mast cells began to accumulate in



Control Group | Treatment Group

Figure 1. The thickness of granulation tissue using 40x magnification and HE staining in the control group (left) and treatment group (left) on the 7th day.

Table 1. Mean thickness of granulation tissue on the 7th day.

	Control	Treatment	P*
7th day	304.43 ± 58,61 µm	215.82 ± 44,73 µm	0.000

*p-value analyzed using two-sample independent T-test

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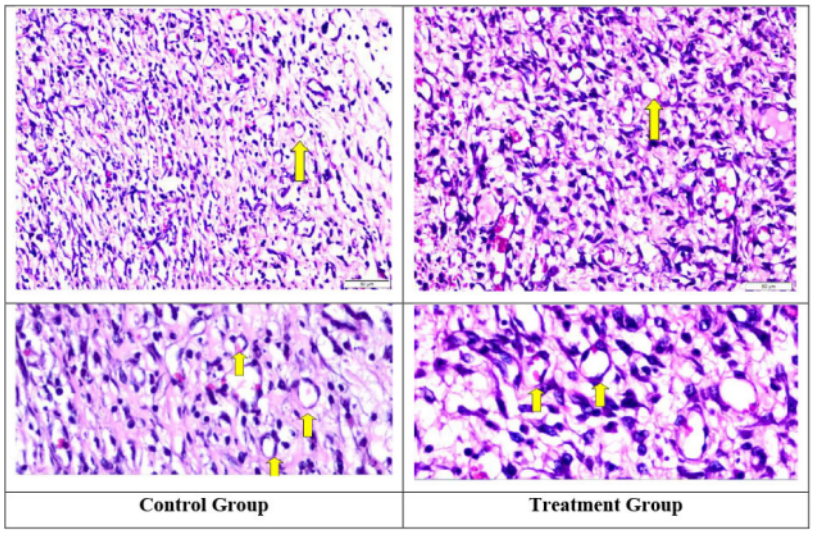

Figure 2. Capillary endothelium (arrows) on 400x magnification and Zoom using HE staining in the control group (left) and treatment group (right) on the 7th day.

Table 2. Mean-rank sum of the number of capillaries in 3 visual fields.

	Control	Treatment	P*
7th day	24.5	8.5	0.0000

*p-value analyzed using Wilcoxon rank sum test (Mann-Whitney)

Table 3. Distribution of collagen density score in both groups.

Score	Control	Treatment	p-value*
0	0	2	
1	1	10	
2	9	4	
3	4	0	
4	2	0	
Mean-rank sum	22.8	10.2	0.0001

*P-value analyzed using *Kruskal-Wallis rank test*

greater numbers in the wound area.[2] This process lasts until the 10th day. During this period, products of mast cell degranulation (histamine, heparin, and various cytokines) can stimulate fibroblasts and promote granulation tissue formation.

In previous studies, the effect of antihistamines on this process has been studied in vivo using topical preparations and in vitro. Antihistamines can stabilize mast cell membranes and inhibit the release of histamine from mast cells. In addition, histamine-induced inflammation can be prevented by preventing the binding of histamine to the H1 receptors of effector cells.[3,4]

The results of statistical analysis in this study showed that the number of capillaries in the treatment group was almost 2 times smaller than in the control group. This proves that antihistamines given orally are also effective in inhibiting the neovascularization process that occurs at the stage of granulation tissue formation.

Angiogenesis is an important part of wound healing, which involves the induction of proinflammatory cytokines and various growth factors.[5] Histamine has a key role in endothelial cell proliferation and angiogenesis by activating H1 and H2 receptors.

The inhibitory effect of antihistamines on the process of angiogenesis, especially in the first 7 days of wound healing, shows its effectiveness in the inflammatory phase and early in the proliferative phase. According to previous studies, antihistamines were more effective in the acute phase than in the advanced phase of wound healing in preventing scar formation.[6]

Decreased angiogenesis will also have an impact on the formation of granulation tissue. In previous studies on hyper-granulation tissue, an imbalance of matrix metalloproteinases, laminin, and excessive angiogenesis has been reported as a cause of hyper-granulation.[7] Therefore, one method of preventing hyper-granulation is to reduce the level of angiogenesis.[8]

There are two hypotheses explaining the effect of histamine on collagen synthesis.[9] First, histamine increases collagen synthesis by promoting vasodilation of blood vessels in the wound and increasing blood supply to granulation tissue. Second, histamine can increase collagen synthesis by directly stimulating cells in the granulation tissue to synthesize extracellular matrix.

Histamine can accelerate the production and polymerization of collagen in granulation tissue in guinea pigs and rats. The rate of wound healing was also found to be inversely related to the level of histamine present, which appears to have an important role in the wound-healing process.[9]

Research by Wolak *et al.* demonstrated that collagen content increased as a result of the direct effect of histamine, both in myofibroblasts and in cell cultures that were not stimulated by injury. The histamine effect works in influencing the synthesis or breakdown of post-transcriptional proteins.[9]

Prolonged stimulation of fibroplasia and angiogenesis can lead to the formation of hyper-granulation tissue, which is problematic for wound healing.[8]

Existing research has examined a lot about the function and contribution of histamine toward wound healing. However, the administration of antihistamines orally on the formation of granulation tissue has never been studied before.

The role of histamine has been investigated in vitro in several studies. In one in vitro study, fibroblasts cultured from normal skin and skin with keloids showed increased proliferation when exposed to histamine.[10] Histamine-induced gene

expression in fibroblasts in cell culture increases the synthesis of type 1 collagen. Moreover, in vitro, histamine-induced collagen type 1 expression in dermal fibroblasts was dramatically inhibited by emedastine difumarate.[11-15] Several other studies have also investigated the effect of antihistamines on cell culture.[4,9]

CONCLUSION

Oral preparations of antihistamines can inhibit the formation of granulation tissue in full-thickness wounds, reduce collagen density, and also decrease angiogenesis.

In this study, the administration of oral antihistamines has the potential to prevent the formation of hyper-granulation tissue by intervening in the wound-healing process. However, its use is not yet common because it is associated with higher side effects than topical administration.

Therefore, further research is needed to compare the effectiveness of oral and topical antihistamines in preventing granulation tissue formation. It is necessary to weigh the advantages and disadvantages of using oral antihistamines.

RESEARCH ETHICS

This research has been approved by the Animal Care and Use Committee, Faculty of Veterinary Medicine, Universitas Airlangga, with ethic number 2.KE.099.08.2022 and has carefully studied the proposed animal use protocol.

CONFLICT OF INTEREST

There is no conflict of interest in writing this research report.

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AUTHOR CONTRIBUTION

All authors have made the same contribution in writing the report on the results of this study, from the stage of proposal preparation, data search, and data analysis, to the interpretation of research data and presentation of the final report.

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