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Short Communication

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Phenethylamine Does Not Accelerate Healing in *Staphylococcus aureus*-infected Wounds in Mice

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ABSTRACT

OBJECTIVE Bacterial infections can lead to a delay in the wound healing process. Recent studies have reported that trace amines accelerate wound healing by enhancing keratinocyte migration thus promoting a faster wound re-epithelization process. This study aimed to investigate the effects of phenethylamine on *Staphylococcus aureus*-infected wounds by using a mouse model.

METHODS This study used mice as a model for in vivo skin wound experiments. *S. aureus* was applied on skin wounds on the backs of the mice. Phenethylamine in different concentrations was also applied either once daily or every two days. The wound diameter, abscess formation, and swollen area were observed every two days for 14 days.

RESULTS Different concentrations and frequencies of phenethylamine applications on the wound exhibited no significant wound healing acceleration. Phenethylamine applications also did not show significant effects on abscess formation or swelling.

CONCLUSIONS *S. aureus* infection may overwhelm the wound healing acceleration effects of phenethylamine resulting in no significant improvement in healing.

KEYWORDS phenethylamine, wound healing, *Staphylococcus aureus*, infection

INTRODUCTION

Bacterial infection in wounds complicates the treatment and significantly hinders the healing process. Infected wounds are often characterized by prolonged inflammation, tissue damage, and an impedimented re-epithelization process. These events can lead to the chronic wound formation (1). *Staphylococcus aureus* (*S. aureus*) is one of the major pathogens causing wound infections (2). *S. aureus* can colonize and invade the injured tissues, trigger the intense inflammation responses, and recruit excessive neutrophils to the wound area (3). The persistence of inflammation and tissues degradation caused by *S. aureus* infection can substantially impede the healing process and increase the risk of abscess formation (3, 4).

Previous publications have reported that trace amines accelerate wound healing in mouse models (5). These compounds, produced by human skin commensals (6), act as partial antagonist of the β-adrenergic receptors, promoting keratinocytes migrations, fibroblasts proliferation, and ultimately accelerate wound closing (7). One of the trace amines, phenethylamine, has shown a potential to boost wound healing in uninfected wounds in a mouse model. This study aimed to investigate the effects of phenethylamine application on *S. aureus*-infected wounds. Using a mouse model, wee valuated

the effects of phenethylamine at various concentrations and frequencies of applications on wound closing, abscess formation, and swelling of the wound area to determine its therapeutic potential in infected wounds.

METHODS

Bacterial preparation for inoculum in wounds

S. aureus USA300 LAC was inoculated into tryptic soy broth medium (TSB) and incubated at 37°C with 200 rpm agitation overnight. The next day, the bacterial cells were pelleted, washed, and resuspended in sterile 0.9% NaCl solution.

Wound experiments in mice

The wound experiments were performed according to a previous publication (5). DDY mice (male, 6-8 weeks, 25-35 gram) were used in this study with 4 mice in each of 10 experimental groups, a total of 40 mice. Prior to the wounding, the mice were anesthetized with ketamine/xylazine (10 : 1) with a dose of 0.04 mg/g mouse weight. The backs of the mice were shaved, and four circular full-thickness wounds (4 mm in diameter) were made on the back skin of each mouse using a skin biopsy punch. The *S. aureus* USA300 suspension was then applied (10 µL) on the wound at 3 x 10^8 CFU. Phenethylamine dissolved at sterile 0.9% NaCl at various concentrations (6.25, 12.5, 25, and 50 µg/mL) was applied topically (10 µL) on the wounds 2 hour after the bacterial infection. The control used in this experiment is the application of sterile 0.9% NaCl. Phenethylamine was applied to the wounds of all the mice either daily or every two days. The wound diameter, abscess formation, and swollen area diameter were observed every 2 days for 14 days.

Statistical analysis

The significance of the wound diameter data was analyzed using the Friedman test with Dunn's multiple comparison test. The data on abscess formation and diameter of the swollen area were analyzed using repeated measures (RM) one-way ANOVA with Tukey's multiple comparisons test. Statistical significance was defined as $p < 0.05$.

RESULTS

The effects of phenethylamine topical application on *S. aureus*-infected wounds were recorded as the wound diameter, the presence of abscess formation and the diameter of the swollen area. The concentrations of phenethylamine were selected based on previous findings that daily application of 25 µg/mL significantly accelerated wound healing in a non-infected model (5). To explore the therapeutic window under infectious conditions, we included both lower and higher concentrations (6.25, 12.5, 25, and 50 µg/mL). In addition, two dosing schedules (daily application and once every two days) were employed to evaluate whether treatment frequency modulates efficacy in *S. aureus* USA300-infected wounds. However, we observed no significant acceleration of wound closing in the experimental animals compared to controls. The application of a high concentration of phenethylamine (50 µg/mL) both every day and every two days decelerated the wound closing significantly (Figure 1A-1B). Abscess formation was observed 2 days post wounding and *S. aureus* infection was observed on the wounds in both the experimental and the control groups, but with varied prevalence. In most cases, the abscess formation was no longer observed after the sixth day with the exception of some mice treated with phenethylamine at concentrations of 12.5, 25, and 50 µg/mL. Statistical analysis showed that treatment with phenethylamine at various concentrations with different application frequencies had no significant effect on abscess formation (Figure 1C). Swelling surrounding the wounds was only observed in the group with phenethylamine application every two days, and no statistically significant difference was observed between the different concentrations of phenethylamine applied (Figure 1D).

DISCUSSION

We observations in this study differ from those in a previous publication (5), e.g., we did not observe a wound closing acceleration effect from the application of phenethylamine on the *S. aureus*-infected wound. This difference could be due to the fact that antagonistic activities of phenethylamine on β-adrenergic receptors in fibroblasts inhibit their proliferation and migration

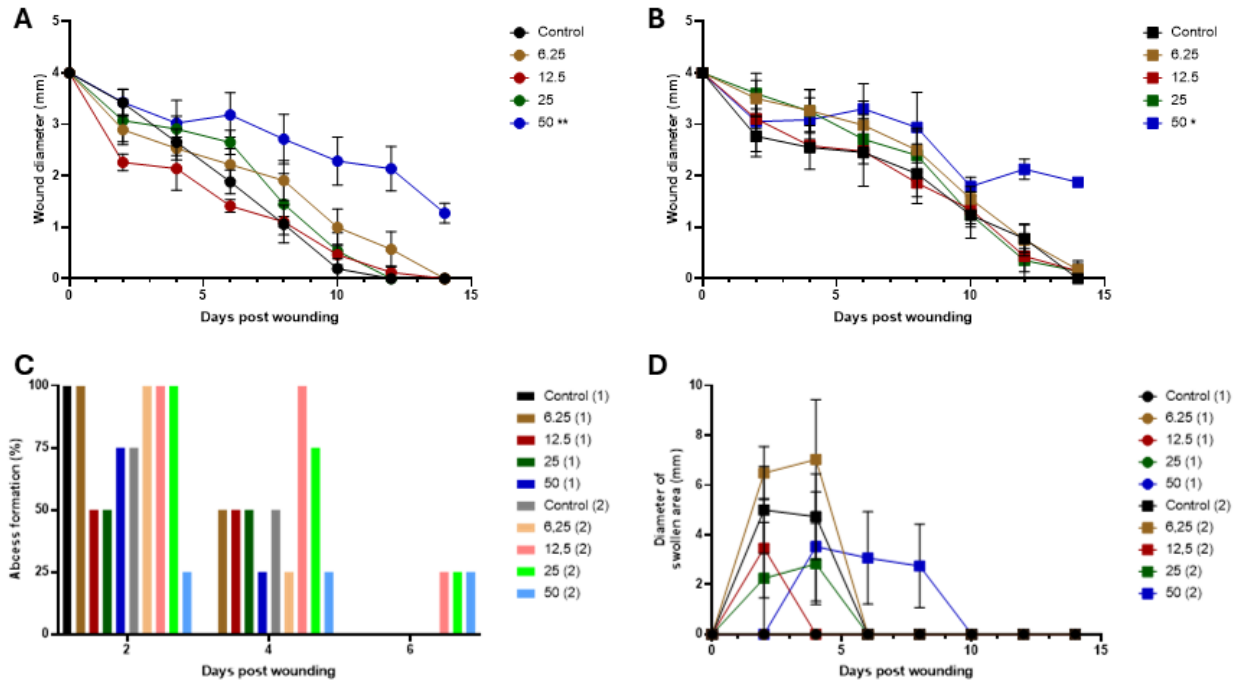

Figure 1. Phenethylamine topical application on *S. aureus*-infected wounds did not show significant affects. Phenethylamine was applied topically at various concentrations on wounds inoculated with *S. aureus* USA300 LAC. The application of phenethylamine did not show any significant enhancement in wound closing between daily application (A) and every two days application (B). Phenethylamine application also showed no significant effect on abscess formation on infected wounds (C) or on the swollen area surrounding the wound (D). The wound diameter data were analysed using the Friedman test, while the abscess formation and swollen area were analysed using repeated measures one-way ANOVA with Tukey's multiple comparisons test. Figure legends represent the concentration of phenethylamine used in the experiments and the number inside the brackets indicates the frequency of phenethylamine application: 1 means daily application and 2 means application every two days. $^{*}p < 0.05$; $^{**}p < 0.01$.

causing a delay in wound healing (7). Moreover, the bacterial infection in wounds can delay healing by triggering a continuous influx of neutrophils to the wound (3, 7, 8). The excessive neutrophils in a wound can lead to further necrosis and extracellular matrix degradation due to the proteases and free oxygen radicals released by neutrophils (9). The presence of excessive neutrophils in the wound leads to the formation of abscess (4), which were observed in all of the treatment groups in this study. The severity of infection induced by *S. aureus* USA300, a highly virulent and invasive strain, may have further masked any potential positive effects of phenethylamine. In a severe infection context, bacterial load and prolonged inflammation are likely the dominant factors determining wound outcome (1, 10-12), overshadowing subtle host-modulatory effects of trace amines.

Swelling, however was observed only in the groups of mice in which the phenethylamine application was done every two days, even in rather than daily, including the control group where only 0.9% NaCl was applied. This suggests that more frequent wound irrigation may help reduce swelling by mechanically removing excess proinflammatory cytokines and cellular debris from the wound area. The irrigation process limits the accumulation of proinflammatory mediators, thereby dampening the inflammatory response and accelerating the transition to the proliferative phase of wound healing. Thus, reducing local cytokine concentrations through more frequent irrigation may help prevent prolonged inflammation and accompanying swelling (13). The virulence factors of *S. aureus* USA300 could possibly override the potential wound healing enhancement effects of phenethylamine. Additionally, infection-associated inflammation may reduce the host responsiveness to trace amines.

This study has some limitations. Only one bacterial strain and one infection model were tested, and the duration of treatment was relatively short. It is possible that different dosing regimens, longer treatment courses and/or co-administration with

antibiotics could yield different outcomes. Moreover, while phenethylamine concentrations were selected based on previous studies in non-infected wounds, their efficacy may vary under infectious conditions where pharmacodynamics and host–pathogen interactions are altered.

Future studies should investigate whether phenethylamine might exert synergistic effects when combined with standard antimicrobial therapy, whether its activity differs with other *S. aureus* strains or less virulent pathogens, and whether modified dosing strategies can improve therapeutic efficacy. These investigations will be important to clarifying the translational potential of phenethylamine in infected wound healing.

CONCLUSIONS

This study demonstrates that topical application of phenethylamine at various concentrations does not significantly affect wound closure, abscess formation, or swelling in *S. aureus*-infected wounds. The severity of infection and associated inflammatory response likely outweighed potential wound-healing effects, possibly compounded by antagonistic actions of phenethylamine on fibroblast β-adrenergic receptors. While limited to a single strain and treatment regimen, these findings highlight the importance of evaluating candidate therapies under clinically relevant infectious conditions, and future work should test phenethylamine in combination with antimicrobial therapy under varied infection severities and with extended dosing strategies.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

AUTHOR CONTRIBUTION

H.D.M.: investigation, methodology, data curation, writing – original draft; E.Z.: supervision, validation, writing – original draft; D.H.: supervision, validation, writing – original draft; A.L.: conceptualization, methodology, funding acquisition, resources, supervision, validation, formal analysis, visualization, writing – original draft, writing – review & editing. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

INSTITUTIONAL REVIEW BOARD STATEMENT

The wound healing experiment using mice were approved by the Ethic Commission of Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia (No. 3.KE.091.10.2020).

INFORMED CONSENT STATEMENT

Not applicable

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