Clinical Efficacy of *Andrographis paniculata* Extracted Scrub Compared With 4% Chlorhexidine Scrub in Burn Wounds: A Prospective Randomized Controlled Trial

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ABSTRACT

Objective: The primary objective of this study is to compare the healing rate between AP soap and 4% Chlorhexidine solution in superficial second-degree burn wounds. The secondary objectives include the analgesic effect and moisturization of these two products.

Materials and Methods: Data was collected between 2019 and 2021. Patients aged 18 years and above, with superficial second-degree burns including at least 20% of TBSA, and admitted to the Burn Unit within 24 hours of injury were included. They were randomly assigned to two groups: *Andrographis paniculata* with Perilla oil liquid soap group (AP group) and 4% Chlorhexidine group (control group). The measurements included percentage of epithelialization, pain score during wound cleansing, itching score after wound cleansing, and dry skin specified symptoms. All patients received standard care for burn wound treatment.

Results: A total enrollment was 23 patients in this study (12 in the AP group and 11 in the control group). The median age was 38.5 years. There were no statistically significant differences in age, %TBSA, and initial wound size between both groups ($p > 0.05$). Although the healing time was similar in both groups, (18.5 vs. 20.1, p=0.347), the AP group had a significantly lower pain score than the control group (4.7 vs. 5.4, p=0.020). Moreover, the AP group demonstrated significant improvements in itching score and SRRC score at 14 days compared to the control group (5.1 vs. 6.0, p 0.039 and 1.08 vs. 1.55, p 0.020, respectively). There were no adverse effects during this study.

Conclusion: Patients treated with *Andrographis paniculata* with Perilla oil liquid soap experienced less pain and better moisturization compared to those treated with the standard 4% chlorhexidine solution, while achieving a comparable healing rate. A future large-scale prospective trial is recommended.

Keywords: *Andrographis paniculata*; wound cleansing; second degree burn (Siriraj Med J 2023; 75: 809-816)

INTRODUCTION

Superficial second-degree burn wounds primarily affect the epidermis and superficial dermis.[1] The dermal layer has the ability to produce epithelial cells in order to replace the lost ones, leading to complete epithelialization of wounds within 3 weeks[2] without any surgical intervention. The primary objective of burn wound care is to achieve rapid wound closure. The treatment involves wound cleansing for optimal wound bed preparation and application of temporary dressings, and infection prevention to create

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https://doi.org/10.33192/smj.v75i11.264451

a protective environment that facilitates the normal wound healing process.[3-5]

Wound bed preparation plays a crucial role in wound management as it enables assessment and treatment of patients with wounds. Wound cleansing is an integral component of wound bed preparation as it leads to an optimized wound environment by removing debris, reducing bacterial load, preventing biofilm activity and maintaining wound moisturization.[6] The standard cleansing treatment for burn wounds has been the use of 4% Chlorhexidine solution. It has a wide range spectrum of anti-bacterial effects and serves as a prophylactic agent against infections of burn wounds - serious problem that can lead to conversion of partial-thickness to full-thickness burn wounds. Literature recommends the use of Chlorhexidine to maintain wound disinfection[6], and two publications suggesting its use only for superficial burns wounds.[7,8] However, the disadvantages of Chlorhexidine solution include pain during wound cleansing and tissue irritation in individuals with dry skin that can potentially delay the wound healing process.[9,10]

Andrographis paniculata known as Fa-Ta-Lai-Jone, is a medicinal plant listed on the World Health Organization's (WHO) 2002 catalogue.[11] It has anti-oxidant properties[12] and exhibits antimicrobial and anti-inflammatory effects[13,14] Phytochemical analysis of extracted *A. paniculata* has revealed that it has several bioactive molecules, for example, andrographolides and flavonoids.[15] These phytochemical constituents may contribute to the plant's wound-healing activity. Andrographolide - the main compound of *Andrographis paniculata* has been reported to decrease inflammation[14,16] caused by dimethyl benzene, histamine, and adrenaline.[17,18] It also demonstrates significant antibacterial activity in its extracted solution.[19,20] Flavonoids, which are known for their antimicrobial properties, have been found to promote the wound-healing process by enhancing wound contraction and epithelialization.[21]

Perilla oil has been shown to suppress production of chemical mediators involved in allergic pathways and inflammatory responses. Essential fatty acids present in Perilla oil offer a wide range of benefits, including anti-inflammatory, antimicrobial, and anticancer properties. In vivo, polyunsaturated omega-3 fatty acids are primarily metabolized into docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are incorporated into cell membranes throughout the body. These specific omega-3 fatty acid metabolites play a role in preventing abnormal clotting, reducing inflammation, relaxing blood vessels, and improving ventilatory parameters.[22]

Therefore, *Andrographis paniculata* with Perilla oil liquid soap (AP soap) is a novel product used for wound cleansing and moisturizer, with potential pain-relieving properties. However, there is a lack of published data regarding its effectiveness in treating burn patients. The objective of this study is to assess the clinical efficacy of AP soap in promoting the healing of superficial second-degree burns, in comparison to the standard cleansing, 4% Chlorhexidine solution.

MATERIALS AND METHODS

A prospective, randomized controlled trial was designed, involving 23 patients who were admitted to the Burn unit at Siriraj Hospital between June 2019 and February 2021. Ethical approval for this study was obtained from the Siriraj Institutional Ethical Review Board (SIRB) (COA no. Si 684/2019). Written consent was obtained from all participating patients after providing them with detailed information. The inclusion criteria was patients between 18 and 60 years of age, presenting with superficial second degree burns within 24 hours of sustaining the injury. The burn wounds covered areas at least 20% of the total body surface area (TBSA). Patients who have underlying medical conditions that could affect the wound healing process such as diabetes mellitus, end-stage renal disease, post-radiation therapy, immunosuppressive drug use, or immunocompromised diseases were excluded, as were pregnant or lactating individuals and those with known hypersensitivity to herbal products. The patients were randomly assigned to one of two treatment groups: the Andrographis and Perilla oil liquid soap (AP soap) group (12 patients) and 4% Chlorhexidine-treated group (11 patients). Demographic data including gender, age, causes of burn, %TBSA, and initial wound area were collected. All patients received initial treatment and underwent wound examination by experienced burn surgeons and nurses who were blinded to the assigned treatment group. The patients were treated following standard burn wound care treatment protocol and wound cleansing procedure as flow chart described in Fig 1 below.

1. Wound bed preparation

The wounds were cleansed using sterile normal saline solution and wrapped to remove excessive discharge from the wound.

2. Wound assessment

The wounds were evaluated. Unfavorable clinical symptoms, complications, or side effects were reported to burn surgeon. A nurse, who was not part of the treatment team, obtained the wound size by placing a sterile transparent

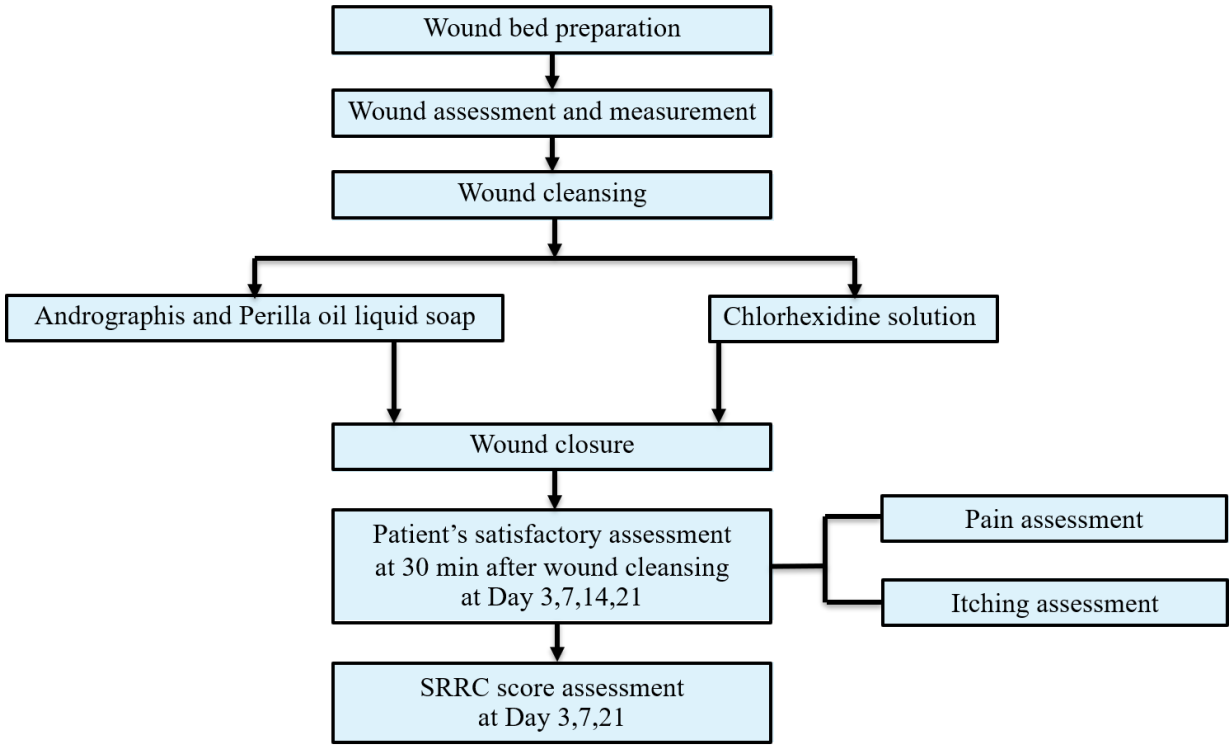

Fig 1. Study protocol.

film on the wound base and measuring its dimensions using a 0.4 mm pinpoint marker. The wound size was recorded. Wound healing was quantified as a percentage of epithelialization, following a previously established protocol[23] using the formula below

$$\%\text{Epithelialization} = \frac{(\textit{Area of initial wound} - \textit{Area of wound at examination date})}{\textit{Area of initial wound}} \times 100$$

3. Wound cleansing

Wound cleansing was performed using either AP soap or a 4% Chlorhexidine solution, based on the assigned treatment group.

4. Wound closure

Sterile gauze was applied to the wound and secured with adhesive tape as per the standard treatment.

5. Pain assessment

Patients were asked to rate their pain levels at thirty minutes after wound dressing using the "Pain Numeric Rating Scale 0-10" on Days 3, 7, 14, 21 of treatment.

6. Itching assessment

Patients were asked to rate their itching score at 30 minutes after wound dressing using the "Itching Visual Analog Scale 0-10" on Days 3, 7, 14, 21 of treatment.

7. SRRC score assessment

Experienced burn surgeons and nurses evaluated the specified symptoms of dry skin at Days 3, 7, 14 of the treatment.

Critically ill-patient treatments, such as volume resuscitation, nutrition, and analgesia were same administered in both groups following standard approach.

The primary outcome of this study was to compare the treatment outcomes of *Andrographis paniculata* extract scrub and 4% Chlorehexidine scrub in the healing of superficial second-degree burn wounds, specifically in terms of healing time and the percentage of gross epithelialization. The secondary outcomes were as follows:

- To compare pain between the two treatments: as rated by patients using the "Pain Numeric Rating Scale 0-10" (scaling on a straight line from 0 to 10 where 0 = no pain, 5 = moderate pain, and 10 = worst possible pain).
- To compare wound moisturization after wound cleansing, assessed using the "Itching Visual Analog Scale 0-10" (scaling on a straight line from 0 to 10 where 0 = no itching; 1-3 = mild itching, 4-6 = moderate itching, and 7-10 = severe itching) and SRRC rating score (assess dry skin-specific symptoms such as scaling, roughness, redness and cracks after wound cleansing).

Statistical analysis

Statistical data analysis was conducted using SPSS version 18.0. Student's t-test was used to assess the difference in means, while the $\chi 2$ test was utilized to determine relationships between parameters. All p values were two-sided. Statistically significant was considered as p values less than 0.05. Kaplan-Meier analysis was performed to compare the healing time between two groups.

RESULTS

A total of twenty-three patients were included in this study, with random allocation into two groups: the AP group consisting of 12 patients, and the control group comprising 11 patients. The median age of all patients was 38.5 years. In the AP group, 66.7% of patients were male, while in the control group, the percentage was 63.6%. Scald burns were the predominant cause in both groups, accounting for 75% in the AP group and 63% in the control group. The mean total body surface area (TBSA) affected was 33% and 35% in the AP and control groups respectively. The mean initial wound size was 171 and 157 square meters in the AP and control groups, respectively. There were no statistically significant differences in sex, age, cause of burn, %TBSA, and initial wound area between the AP and control groups ($p > 0.05$). The demographic data is shown in Table 1 below.

The mean healing time in the AP soap-treated group was 18.5 days, while it was 20.1 days in the control group. There was no statistically significant difference in healing time between these two groups (p 0.347). All patients in this study achieved complete epithelialization of their wounds within 4 weeks after injury. The percentage of gross wound epithelialization on day 14 was statistically significantly higher in the AP soap-treated group compared to the control group, with values of 87% and 82%, respectively (p-value of 0.027). On day 21, the percentage of gross wound epithelialization was 97.8% in the AP soap-treated group and 96.77% in the control group, with a p-value of 0.58. Tables 2 provides details on the percentage of epithelialization. Kaplan-Meier analysis demonstrated no statistically significant difference in wound epithelialization between the two groups as shown in Fig 2. The healing time after treatment was 18 and 20 days, respectively, with no statistically significant difference. Hospital stay did not significantly differ between the two groups (46.7 and 50.5 days, p-value = 0.64). There was no instance of burn wound infection among the patients.

TABLE 1. Demographic data.

	AP soap group (n=12)	Control group (n=11)	P-value
Male patient (%)	8 (66.7)	7 (63.6)	0.879
Age (years ± SD)	40.33 ± 14.69	36.55 ± 12.93	0.520
Cause of burn			0.554
Frame burn (%)	3 (25.0)	4 (36.4)	
Scald burn (%)	9 (75.0)	7 (63.6)	
%TBSA (percent ± SD)	33.8±14.3	35.6±15.2	0.762
Initial wound area (cm^2± SD)	171.0 ± 29.6	157.2 ± 36.7	0.331

TABLE 2. Percent epithelialization at days 3, 7, 14, 21 after treatment, healing time, and length of stay.

	AP soap group	Control group	P-value
% Epithelialization			
Day 3	3.68±1.42	3.05±1.10	0.256
Day 7	28.65±4.69	26.75±5.06	0.361
Day 14	87.39±4.65	82.55±5.14	0.027
Day 21	97.80±4.06	96.77±4.73	0.581
Healing time	18.5 ± 4.0	20.1 ± 3.9	0.347
Length of stay (Days)	46.7±18.8	50.5±20.8	0.643

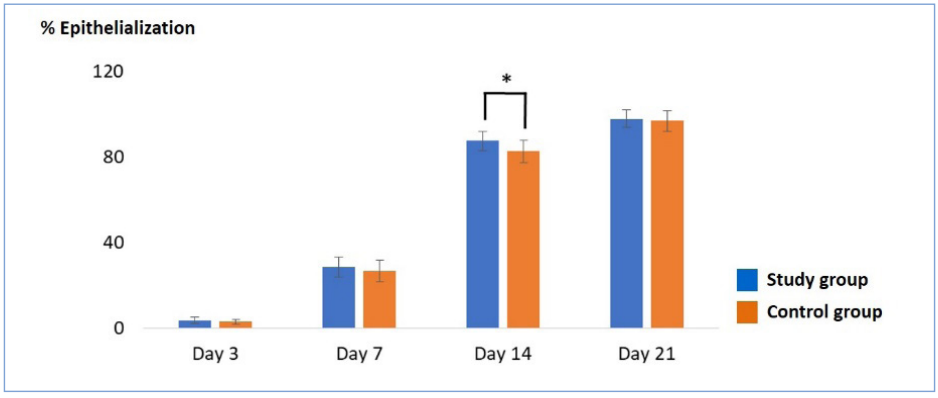

Fig 2. Percent Epithelialization on days 3, 7, 14, 21 after treatment

Pain assessment during wound cleansing

The mean of pain analog scores assessed between the AP soap-treated group and the control group during the initial treatment period (days 1-3) showed no significant differences. However, the pain score was significantly lower in the AP soap-treated group at 7 days (4.7 vs. 5.4, p=0.020), and 14 days (2.6 vs. 3.5, p=0.011) after treatment, as shown in Table 3.

Wound moisture after wound cleansing

The AP soap-treated group demonstrated a significant improvement in itching score, indicating enhanced wound moisturization at 14 days compared to the control group (5.1 vs. 6.0, p=0.039). Although the SRRC score could not be evaluated during the first 3 days after treatment due to excessive wound discharge, the, the AP soap group exhibited a significantly lower SRRC score than the control group at 14 days post-treatment treatment (1.08 vs. 1.55, p=0.020). Table 3 presents the pain score, itching score, and SRRC score.

Cases demonstration

Patients received standard care for burn wound treatment, with the exception of the cleansing process which depended on the assigned treatment group. The procedure for wound cleansing using AP soap is demonstrated in Fig 3. An example of wound healing progression using AP soap is shown in Fig 4.

TABLE 3. Percent epithelialization at days 3, 7, 14, 21 after treatment, healing time, and length of stay.

	AP soap group	Control group	P-value
Pain score			
Day 0	6.0±1.1	5.9±1.4	0.864
Day 3	6.0±0.9	6.0±1.1	1.00
Day 7	4.7±0.5	5.4±0.8	0.020
Day 14	2.6±0.7	3.5±0.8	0.011
Itching score			
Day 0	2.9±1.0	3.1±1.1	0.850
Day 3	3.1±0.9	3.3±1.1	0.655
Day 7	4.5±0.7	4.8±0.9	0.337
Day 14	5.1±1.0	6.0±1.0	0.039
SRRC score			
Day 0	N/A	N/A	N/A
Day 3	N/A	N/A	N/A
Day 7	1.33±0.49	1.45±0.52	0.573
Day 14	1.08±0.29	1.55±0.52	0.020

Fig 3. The application of AP-soap started with rinsing AP soap. Wet gauze was used for scrubbing and then the wound was cleaned.

A. Day3 B. Day7 C. Day14

Fig 4. Example of an AP soap treatment group patient.

DISCUSSION

The use of Chlorhexidine solution as a standard topical wound cleansing treatment for partial thickness burns has been established for decades. However, there are some disadvantages such as wound base tissue irritation and pain during wound cleansing.[10,24] This study aimed to evaluate the clinical efficacy of *Andrographis paniculata* and Perilla oil liquid soap (AP soap) in the healing of superficial second-degree burn wounds. The results demonstrated comparable wound healing outcomes with reduced pain during wound cleansing, and more moisturization compared to the standard cleansing Chlorhexidine solution. Thus, AP soap appeared to address the disadvantages associated with Chlorhexidine solution. *Al-Bayaty et al*, reported the effects of topically applied *A. paniculata* leaf extract on wound healing in rat models. The macroscopic examination revealed the significantly faster wound healing rate in rats with extracted *A. paniculata* dressing compared to placebo.[25] This study showed no significant differences in time required to complete gross epithelialization, representing the healing time of burn wounds, between the AP soap-treated group and 4% Chlorhexidine-treated group (control group), which were 18.5 days and 20.1 days, respectively (p=0.347). However, on day 14 of treatment, the epithelialization rate was higher, suggesting that AP soap may accelerate the wound healing process. No significant difference was found on day 21, as wounds tended to heal naturally, and the small sample size may have contributed to the lack of statistical significance. Significant differences may be identified in a randomized controlled trials with larger number of enrolled patients. This study also reported no significant differences in the length of stay between the groups (AP soap 46.7 ± 18.8 vs. Control group 50.5 ± 20.8, p= 0.643). No adverse side effects of AP soap were observed in this study.

Pain management remains a challenging aspect in burn patient care. Recurrent pain exposures in burn patients can lead to secondary hyperalgesia and contribute to chronic pain issues, significantly affecting quality of life.[26] Wound cleansing, in particular, is a procedure that can produce severe pain, as patients often have to endure it more frequently compared to other treatments. Previous studies have explored several of methods and wound cleansing products to address this problem. Although achieving completely pain-free wound cleansing products remains elusive, advancements in dressing material have shown promise in reducing pain and discomfort during wound dressing changes. Our study demonstrated that pain during wound cleansing was significantly lower in the AP soap treated group compared to the 4% Chlorhexidine–treated group at 7 days and 14 days after treatment, during the period when wounds had not fully epithelialized. This finding was supported by

patient experiences and the numeric pain score ratings, indicating that AP soap was less painful and provided a more comfortable experienced for patients.

For optimal wound healing, a moist environment is known to facilitate faster and less painful hearing compared to a dry environment, which can lead to cell dehydration and death. This often results in the formation of a scab or crust over the wound, hindering healing. By maintaining proper hydration with a moisture-retentive dressing, migration of epidermal cells is enhanced, encouraging epithelialization.[9] The itching visual analog scale, as suggested by *Reich, et al*[27] is an appropriate parameter for evaluating skin conditions. In this study, the itching visual analog scale demonstrated significantly lower scores in the AP soap-treated group compared to the control group at 14 days after treatment (5.1 vs. 6.0, p=0.039), indicating improved moisturization with AP soap.

The specified symptom sum score (SRRC) system, acknowledged by the European group on Efficacy Measurement of Cosmetics and other topical products (EEMCO), assesses skin-specific symptoms such as scaling, roughness, redness, and cracks or SRRC; to evaluate the effects of topical products.[28,29] In this study, statistically significant improvements in the SRRC rating score were observed in the AP soap-treated group at 14 days after treatment (p-value 0.020).

This research was conducted in randomized controlled trial design to reduce bias. However, the small sample size limited the ability to detect significant differences in certain measurements. These findings highlight the need for well-designed studies to further investigate the efficacy of the *Andrographis paniculata* and Perilla oil liquid soap as a wound cleansing agent for partial thickness burn wounds. A future large prospective study is warranted.

CONCLUSION

Andrographis paniculata and Perilla oil liquid soap, a novel natural product for epithelialization of wounds demonstrated comparable wound healing rates to chlorhexidine solution, with the added benefits of reduced pain and better moisturization.

Declaration of conflicting interests

The author(s) declare no potential conflicts of interest according to the research, authorship, and/or publication of this article.

ACKNOWLEDGEMENTS

The authors would like to thank the Burn Unit, Division of Trauma Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Thailand for their support and dedicated care of patients.

The authors would like to express our gratitude to the dedication of Assoc. Prof. Dr. Watcharee Khunkitti for being consultant of soap product development.

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