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Original Research Article

Comparison of the Therapeutic Effects of 2% *Areca catechu* Gel and 0.1% Triamcinolone Acetonide in Patients with Recurrent Aphthous Stomatitis: A Randomized Clinical Trial

Liza M. Sari[1]*, Sri Rezeki[1], Munifah Abdat[2]

[1]*Department of Oral Medicine, Faculty of Dentistry, Universitas Syiah Kuala, Banda Aceh, Indonesia;*
[2]*Department of Public Health, Faculty of Dentistry, Universitas Syiah Kuala, Banda Aceh, Indonesia*.

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ABSTRACT

Areca catechu L. (*A. catechu*) or areca nut contains the main phytochemical compounds arecoline and catechin. It also possesses high antioxidant properties and can be used as a medication. Thus, this study was conducted to compare the therapeutic effects of 2% *A. catechu* gel and 0.1% triamcinolone acetonide on recurrent aphthous stomatitis (RAS). Overall, 46 randomly selected patients were divided into *A. catechu* gel and triamcinolone acetonide treatment groups. The topical preparations were applied to oral lesions three times daily in each group. Ulcer diameter, discoloration, pain intensity, and quality of life were assessed for 7 days, with ulcer size and pain intensity analyzed on day 7. Consequently, the *A. catechu* gel and triamcinolone acetonide demonstrated therapeutic effects after 7 days of treatment. The topical treatments examined did not show a significant difference in alleviating pain and reducing erythema associated with the ulcer. Furthermore, no correlation was found between ulcer diameter and pain intensity in *A. catechu* and triamcinolone acetonide. *Areca catechu* gel promoted RAS healing owing to its analgesic and anti-inflammatory properties.

Keywords: *Areca catechu*, Discoloration, Ulcer Diameter, Quality of Life, Recurrent Aphthous Stomatitis, Triamcinolone Acetonide.

Introduction

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal disorder, affecting 25% of the global population and approximately 12% of the Indonesian population.[1] The lesion is a round or oval ulcer with a yellowish-gray pseudomembranous center surrounded by an erythematous border.[2] Recurrent aphthous stomatitis is mainly caused by antibody-dependent cellular cytotoxicity, specifically direct T lymphocyte-mediated cytotoxicity, which destroys the oral mucosa. Other causes include allergies, trauma, stress, infectious agents, systemic conditions with RAS-like ulcer, hormones, hematologic abnormalities, nutritional deficiencies, and genetic predisposition.[3] The main principles for RAS treatment include reducing the severity of lesions, relieving symptoms, shortening the healing time, using prophylaxis agents against recurrence, and controlling risk factors.[4] Clinically, analgesics, antibiotics, and corticosteroids are used topically to treat RAS. However, prolonged and frequent use of chemical agents may increase the risk of fungal infections and drug resistance, potentially leading to more severe adverse effects and fatal outcomes.[5]Chlorhexidine gluconate mouthwashes and topical corticosteroids can have several adverse effects, such as disruption of oral cavity homeostasis and significant cytotoxicity toward human fibroblasts, myoblasts, and osteoblasts.[6]

*Corresponding author. E mail: lizameutiasari@usk.ac.id
Tel: +6287886497414

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Other stronger medications, such as antitumor necrosis factor (TNF), thalidomide, colchicine, pentoxifylline, and dapsone, also have side effects, such as nausea, minor gastrointestinal pain, fatigue, dizziness, diarrhea, headache, lethargy, jaundice, hemolysis, and decreased hemoglobin levels, specifically when used for >6 months.[7] Although some drugs are effective in healing RAS ulcers, clinicians should be cautious about their chronic use.

Topically applied mucosal protectants derived from herbal ingredients have been made as alternatives to chemical drug-based treatments. These protectants create a temporary physical barrier over the ulcerous lesion, thereby reducing inflammation and alleviating pain.[8-10] Different plants with anti-inflammatory, antioxidant, and analgesic activities were examined for use as alternatives to minimize the side effects caused by chemical-based drugs.[11-13] For example, areca nut, or *Areca catechu* L. (*A. catechu*), is a herbal plant that shows potential as a topical medicine. *Areca catechu* grows abundantly and is chewed as an appetizer in traditional ceremonies to welcome guests. Previous studies have shown that *A. catechu* possesses therapeutic properties as an antioxidant [14-16], antibacterial[17], antiaging[18], analgesic[19], antihelmintic[20], anti-inflammatory[21], antiproliferative[22], and anticancer.[23] *Areca catechu* may be used in treating oral cavity lesions. Several clinical trials have shown that topical oral gels containing herbal plant-derived ingredients promote healing of lesions and alleviate pain without causing side effects.[24-26] Therefore, this study aimed to explore and compare the therapeutic effects of 2% *A. catechu* extract in topical gel preparations with those of 0.1% triamcinolone acetonide on RAS lesions

Materials and Methods

The treatment group used *A. catechu* oral gel containing 2% *A. catechu* extract as the active ingredient and carboxymethyl cellulose-natrium, propylene glycol, glycerin, and methylparaben. The positive control group used Kenalog in orabase containing 0.1% triamcinolone acetonide, gelatin, pectin, carmellose sodium, and plastibase. These preparations were packed into 5 mg white tubes. Each tube was

assigned a number for blinding, and two investigators administered them to the patients.

Participants and research design

This clinical study employed a randomized double-blind case-control design to investigate the therapeutic effect of *A. catechu* gel on ulcer diameter, color changes, pain intensity, and quality of life. The correlation between pain intensity and changes in ulcer size was also investigated before and after treatment. This single-center clinical trial was conducted at the Oral and Dental Hospital, Faculty of Dentistry, Universitas Syiah Kuala, Banda Aceh, Indonesia. All procedures followed the guidelines of the Declaration of Helsinki[27] and were approved by the Ethical Committee Board of Universitas Syiah Kuala (No. 76/KE/FKG/2025).

Based on the inclusion and exclusion criteria, 50 patients with complaints of aphthous ulcer referred to the oral medicine clinic were enrolled. These patients were divided into two groups: *A. catechu* gel treatment group and the control group. Following verbal instructions, all patients signed an informed consent form. The *A. catechu* oral gel and the triamcinolone acetonide paste were prepared in white tubes. Patients randomly received either treatment. The diagnosis of RAS was based on anamnesis and clinical examination. The ulcer was round with well-defined borders, surrounded by erythema and a white base, and was located on non-keratinized mucosa in an easily accessible area.

The inclusion criteria were as follows: male and female patients aged 18–60 years, a history of RAS in the last 6 months, with a frequency of once every 2 months, and the appearance of lesions in different locations. The exclusion criteria were as follows: patients who had received cancer treatment within the past 3 months; those receiving oral or topical corticosteroid therapy; individuals with systemic diseases such as Behçet's syndrome, Crohn's disease, or ulcerative colitis with oral manifestations similar to RAS; patients allergic to specific drugs or foods; and individuals with virus-induced oral mucosal diseases or autoimmune disorders.

Data collection

All patient data recorded between December 2023 and May 2024 were collected. The sample size was calculated using a purposive sampling formula. Demographic data were obtained from the subject selection form filled out on day 1. Data regarding oral ulceration were collected on days 1 and 7 through anamnesis and clinical examination to deduce the ulcer diameter, color changes, pain intensity, and quality of life. Patients were instructed to apply *A. catechu* gel and triamcinolone acetonide on dry oral mucosa every 8 hours for 6 days. They were instructed to refrain from eating or drinking 30 minutes after applying the gel or orabase paste to allow adequate absorption into the mucous membrane. This precaution also prevented the gel from being wiped off, swallowed, or mixed with food and beverages, which could reduce the effectiveness or lead to potential side effects.

Ulcer diameter was measured from the outermost side of the erythema circle using a UNC 15 periodontal probe and reconfirmed with clinical photographs. RAS ulcers included were round and divided into three types: completely healed, minor ulcers measuring 1–3 mm, and minor ulcers measuring 4–10 mm. Major ulcer measuring >10 mm and herpetiform-type ulcers were excluded. The degree of discoloration was assessed visually using a mouth mirror and supplemented by clinical photographs. The stages of discoloration observed were as follows: stage 0, no erythema or coloration identical to the normal mucosal surface; stage 1, erythema; stage 2, gray; stage 3, yellow; stage 4, intense gray yellow without erythematous edges; and stage 5, intense gray yellow with erythematous edges.[28]

Pain intensity data were collected using a visual analog scale (VAS) distributed through Google Forms. This scale consists of a 10-cm horizontal line between the poles of "no pain (0)" and "unbearable pain (10)."[29] Patients were asked to mark the number on the horizontal line showing the pain level of the ulcer. Two investigators conducted all evaluations, including ulcer size, color changes, pain intensity, and quality of life. Examinations were performed in the morning between 9:00 and 11:00 am. Patients were asked to report side effects of the gel. Quality of life was assessed using the Short Form-36 (SF-36) questionnaire given on days 1 and 7. This questionnaire includes eight domains: bodily pain, physical functioning, general health, physical role limitations, social functioning, emotional role limitations, vitality, and mental health.[30] Scores were recorded on a five-point Likert scale for each aspect and converted into a 0–100 scale, with a total score >50 points indicating a good quality of life.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA), and the significance level was set at $p < 0.05$. Qualitative and quantitative data were presented as percentages and mean ± SD, respectively. The Wilcoxon signed-rank test was used to compare all parameters before and after treatment. The Mann–Whitney test was employed to determine the difference between the treatment and control groups on day 7. The correlation between pain intensity and ulcer size in both groups was analyzed using the Spearman correlation test

Results and Discussion

Demographic data and ulcer characteristics

A total of 50 patients were eligible to participate in this clinical study. However, four patients in the treatment and control groups dropped out because of their unwillingness to continue. As a result, the treatment and control groups included 25 and 21 patients, respectively. Patients were between 20 and 44 years old, with the mean age of 26.6 ± 6.77 years in the treatment group and 23.6 ± 3.69 years in the control group. The study population was predominantly female, which accounted for 84% and 90.4% of the participants in the treatment and control groups, respectively. Most of the ulcers were located in the lower labial mucosa, followed by the upper labial and buccal mucosa. Minor ulcers measuring 4–10 mm were the predominant RAS type in the treatment and control groups (74.1% and 61.9%, respectively). Yellow and intense gray–yellow ulcers without erythematous edges were most commonly detected in both groups before treatment. After treatment, lesions were predominantly red and gray with normal surrounding mucosal tissue. Before treatment, both groups complained of high-intensity pain. Despite the presence of RAS, patients exhibited good quality of life before and after treatment (Table 1). No patients reported side effects, and some noted that the gel had a sweet taste.

The A. catechu gel and triamcinolone acetonide group demonstrated improvement after 7 days of treatment.

The *A. catechu* gel group exhibited significant healing after 7 days of treatment. This was shown as a reduction in the diameter of the RAS ulcer from 4.21 ± 1.26 to 1.2 ± 0.82 mm, indicating a reduction of 70.07%. The triamcinolone acetonide group also exhibited a similar reduction of 70.74% (4.34 ± 1.27 to 0.17 ± 0.42 mm). The color score reduced significantly after 7 days of *A. catechu* gel application, indicating reduced inflammation. In the *A. catechu* gel group, the discoloration score decreased by an average of 77.27%. Pain intensity measured using the VAS scale, also declined notably from 6.04 ± 2.39 on day 1 to 0.28 ± 0.46 on day 7, representing a reduction of 95.64%. A similar decrease in pain intensity was observed in the triamcinolone acetonide group, with a 97.77% reduction. Although the quality-of-life scores were high both before and after treatment, they still increased from 59.36 ± 21.61 to 83.18 ± 13.40. Table 2 presents an overview of the pretreatment and post-treatment comparison**.**

Topical treatments are effective at alleviating pain and reducing erythema.

No significant difference in ulcer coloration was found between the *A. catechu* gel and triamcinolone acetonide group (0.40 ± 0.50 and 0.19 ± 0.40, respectively) after 7 days.

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Table 1: Ulcer type, discoloration, pain intensity, and quality of life of the participants

		A. catechu gel (%) (n = 25)		TA (%) (n = 21)	
		Day 1	Day 7	Day 1	Day 7
Ulcer type	No ulcer	0	51.9	0	81
	Minor (1–3 mm)	25.9	48.1	38.1	19
	Minor (4–10 mm)	74.1	0	61.9	0
Discoloration	Normal	0	60	0	85.7
	Red/erythema	0	5	0	14.3
	Gray	0	35	0	0
	Yellow	48	0	23.8	
	Intense gray yellow without erythematous edges	28	0	52.4	0
	Intense gray yellow with erythematous edges	24	0	23.8	0
Pain intensity	No pain	0	72	0	85.7
	Low	0	28	0	14.3
	Medium	24	0	19	0
	High	76	0	81	0
Quality of life	Low	32	46.3	19	0
	High	68	53.7	81	100

TA, triamcinolone acetonide.

Table 2: Comparison of ulcer size, discoloration, pain intensity, and quality of life between days 1 and 7

	Groups					
	A. catechu gel (mean ± SD) (n=25)			TA (mean ± SD) (n=21)		
	Day 1	Day 7	*P*	Day 1	Day 7	*p*
Ulcer diameter (mm)	4.21 ± 1.26	1.2 ± 0.82	0.000	4.34 ± 1.27	0.17 ± 0.42	0.000
Discoloration	1.76 ± 0.83	0.40 ± 0.50	0.000	2.00 ± 0.70	0.19 ± 0.40	0.000
Pain intensity	6.04 ± 2.39	0.28 ± 0.46	0.000	6.29 ± 2.05	0.14 ± 0.36	0.000
Quality of life	59.36 ± 21.61	83.18 ± 13.40	0.000	78.68 ± 15.70	92.84 ± 6.40	0.000

$p < 0.05$ for the Wilcoxon signed rank test. TA, triamcinolone acetonide. SD, standard deviation.

Therefore, the treatments demonstrated nearly equal effects on reducing inflammation or erythematous ulcer (Table 3). For pain intensity, both treatments were equally effective in reducing pain (0.28 ± 0.46 and 0.14 ± 0.36, respectively). The effects of *A. catechu* gel and triamcinolone acetonide on ulcer diameter and quality of life were significantly different. Although topical oral preparations significantly reduced the ulcer size, triamcinolone acted more quickly to improve RAS. By day 7, ulcers treated with *A. catechu* gel were larger than those treated with triamcinolone acetonide, measuring 1.20 ± 0.82 and 0.17 ± 0.42 mm, respectively. This finding proved that triamcinolone acetonide could heal ulcers faster than *A. catechu* gel. The quality-of-life scores were significantly higher in the triamcinolone acetonide group than in the *A. catechu* gel group (92.84 ± 6.40 and 83.18 ± 13.40, respectively) (Table 3).

By day 7, no correlation was observed between the ulcer diameter and pain intensity in both the A. catechu gel and triamcinolone acetonide groups.

No correlation was found between ulcer diameter and pain intensity after 7 days of treatment with *A. catechu* and triamcinolone acetonide (Table 4). This study compared the therapeutic effects of *A. catechu* and triamcinolone acetonide on ulcer diameter, color change, pain intensity, and quality of life after 7 days of treatment. To our knowledge, this is the first clinical study using *A. catechu* gel on RAS ulcers. The results showed that minor lesions with diameters <1 cm and clear margins surrounded by a halo erythema were consistently observed in RAS. Minor lesions represent the predominant type, affecting 80% of individuals diagnosed with RAS.[31] In this study, most of the patients with RAS were female. [32] also found that RAS is prevalent in Iranian women, accounting for approximately 60.7% of cases.[32] Women are particularly susceptible to RAS during menstruation and menopause due to hormonal imbalance, deficiencies in vitamins B1, B2, B6, B12, and D, and low levels of iron, folic acid, and zinc.[33]

The topical treatments evaluated exerted therapeutic effects on aphthous ulcers after 7 days of treatment. *Areca catechu* gel was found to reduce the lesion size and inflammation, indicated by the discoloration or erythema. The results of the present study support the findings of that *A. catechu* increased healing by reducing the infiltration of inflammatory cells, preventing coagulative necrosis, increasing the amount of collagen, and promoting the formation of neovascularization in skin burns.[34] Another study reported that *A. catechu* leaves can reduce inflammation by decreasing nitric oxide (NO) generation, inducible NO synthase, and cyclooxygenase-2 (COX-2) expression.

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Table 3: Comparison of the ulcer size, discoloration, pain intensity, and quality of life between *A. catechu* gel and triamcinolone acetonide on day 7

	Groups		
	A. catechu gel (mean ± SD)	TA (mean ± SD)	*p*
	(n = 25)	(n = 21)	
Ulcer diameter (mm)	1.20 ± 0.82	0.17 ± 0.42	0.000
Discoloration	0.40 ± 0.50	0.19 ± 0.40	0.056
Pain intensity	0.28 ± 0.46	0.14 ± 0.36	0.267
Quality of life	83.18 ± 13.40	92.84 ± 6.40	0.000

p <0.05 for the Mann–Whitney U-Test. TA, triamcinolone acetonide. SD, standard deviation.

Table 4: Correlation between ulcer size and pain intensity on day 7 of *A. catechu* gel and triamcinolone acetonide treatment

		Pain intensity on day 7	
		***A. catechu* gel**	**TA**
Ulcer diameter	Correlation coefficient	0.337	−0.166
	p	0.100	0.472

p <0.05 for the Spearman correlation test. TA, triamcinolone acetonide.

In addition to flavonoids, tannins, alkaloids, triterpenoids, fatty acids, alpha-terpineol, vanillin, benzyl alcohol, resveratrol, capric acid, and polyphenols, *A. catechu* contains steroids that can exert anti-inflammatory effects.[35] *Areca catechu* also possesses anti-inflammatory and hepatoprotective properties, making it safe for topical application.[36] In this study, triamcinolone acetonide in orabase was used as the reference standard. This preparation demonstrates anti-inflammatory, antipruritic, and vasoconstrictive activities in ulcerative and inflammatory lesions such as RAS, lichen planus, and lupus erythematosus. Triamcinolone belongs to a class of glucocorticoids categorized as medium- to high-potency corticosteroids. It works by blocking the phospholipase A2 enzyme on the phospholipid layer of cell membranes, which inhibits the breakdown of leukocyte lysosomal membranes and prevents arachidonic acid from exerting its anti-inflammatory and immunosuppressive effects. Triamcinolone also reduces the release of prostaglandins and leukotrienes by inhibiting the activity of COX and lipoxygenase.[37] Furthermore, corticosteroids exert anti-inflammatory effects by reversing arterial dilatation and permeability, which inhibits leukocytes and macrophages from migrating to the affected area. The constriction of blood vessels in the upper dermis reduces the release of inflammatory mediators to the site of injury. The anti-inflammatory effect is also attributed to the synthesis of lipocortin, which inhibits phospholipase A2, thereby reducing the production of prostaglandins and leukotrienes. Topical corticosteroids also enhance the expression of anti-inflammatory genes directly at the DNA level while indirectly inhibiting inflammatory transcription factors, such as NF-kB, which helps decrease the expression of proinflammatory genes.[38] The process can reduce edema, erythema, pain, and ulcer size.

On day 7, triamcinolone acetonide was found to be effective than other therapies in healing aphthous ulcers. The preparation, formulated as an emollient dental paste, has enhanced adhesive properties when applied to wet and mobile mucosal surfaces. Recommended concentrations include 0.025%, 0.1%, and 0.5%, with 0.1% being the most effective.[39] Additionally, factors such as the integrity of the epidermal barrier and use of occlusive dressings can influence the absorption of topical steroids. The presence of mucosal inflammation or ulcers increases drug absorption compared with normal mucosal surfaces. The triamcinolone acetonide paste serves as an occlusive dressing, enhancing the adhesion duration between the paste and ulcer lesions on the moist mucosa, stimulating new tissue formation, retaining moisture, alleviating pain, and preventing infection. Once absorbed by the mucosa, the triamcinolone binds to plasma proteins, is metabolized in the liver, and is excreted by the kidneys.

Topical oral gels can increase local bioavailability and reduce systemic exposure when applied directly to lesions. Owing to its high permeability and rich vascularity, the nonkeratinized oral mucosa promotes rapid absorption of medications. However, factors such as poor adherence, an unpleasant taste or odor, and solubility issues can compromise patient compliance, and rapid salivary clearance, epithelial turnover, enzymatic breakdown, and continuous mucosal movement further limit retention.[40] Gel preparations have several disadvantages, such as the limited ability to adhere to the mucosa for extended periods and ease of dissolution in saliva. Therefore, the healing speed by *A. catechu* gel is influenced by the active chemicals within the gel and is hastened by robust immune response, specifically from sIgA in saliva, adequate vascularization, and good oral hygiene. To address the issue of inadequate adhesive ability, several measures have been implemented. These include applying the gel precisely onto the lesion, advising the patient to avoid speaking for several seconds after application to allow optimal adhesion, refraining from consuming food and drinks for 20–30 minutes after application, consistently applying the gel three times daily, and minimizing contact with the ulcer.

Areca catechu can also reduce pain intensity in RAS ulcers. Although the mechanism is still unclear, its procyanidin content can relieve migraines. Alkaloids also exert a significant antinociceptive or analgesic effect by inhibiting COX-2 expression.[41] *Areca catechu* can also increase the level of neurotransmitters and brain-derived neurotrophic factors.[42] In this study, no correlation was found between pain and ulcer size. Pain may be more related to the severity of inflammation. Ulcer healing stimulates the restoration of tissue integrity, physiologically divided into four phases: hemostasis, inflammation, proliferation, and tissue remodeling. Inflammatory pain arises from the activation of inflammatory cells such as glial cells, macrophages, and lymphocytes, releasing TNF-α and interleukin-1β.[43] Although oral gels were found to decrease inflammation and pain levels, these interventions do not adequately stimulate tissue repair, as evidenced by ulcer size reductions.

The analysis using SF-36 showed that the patients had a good quality of life before and after treatment because the ulcers were morphologically classified as minor, single lesions, predominantly located on the lower labial mucosa. According to RAS can affect the quality of life, depending on the number and size of the ulcer.[30] In the present study, the effectiveness of *A. catechu* gel for treating RAS was evaluated. However, limitations remain, such as a lack of patient discipline,

analysis of a small sample, inadequate follow-up period, and drug dosage. The self-limiting nature of RAS also affects the outcome. In this context, ulcer healing may occur naturally through the self-repair mechanisms of the body and improved immune response.

Conclusion

In this study, 2% *A. catechu* oral gel and 0.1% triamcinolone acetonide demonstrated therapeutic effects after 7 days of treatment. These topical treatments demonstrated comparable effects on reducing pain and erythema. Furthermore, no correlation was found between ulcer diameter and pain intensity on day 7 of treatment with *A. catechu* and triamcinolone acetonide. Considering the limitations of this study, higher-quality clinical trials that involve a larger sample size, an adequate follow-up period, and clinical assessments are needed to evaluate the effectiveness of *A. catechu* oral gel application on RAS.

Conflict of Interest

The author declares no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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