Vol. 37 / No. 3 / December 2025
Sinta 2 (Decree No: 200/M/KPT/2020)
Online ISSN : 2549-4082 ; Print ISSN : 1978-4279
Available online at https://e-journal.unair.ac.id/BIKK

Berkala Ilmu Kesehatan Kulit dan Kelamin

Original Article

Periodical of Dermatology and Venereology

Comparison of the Effectiveness of Topical 5-Fluorouracil, Topical Calcipotriol, and Liquid Nitrogen Cryosurgery in Seborrhoeic Keratosis

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ABSTRACT

Background: Seborrhoeic keratosis (SK) is a benign tumor composed of epidermal keratinocytes occurs most frequently in the elderly. The action of 5-fluorouracil (FU) cream and calcipotrienes on keratinocyte development and has been shown beneficial for SK. **Purpose:** To compare the effectiveness of 5-FU and calcipotriol topical with cryosurgery. **Methods:** Eighteen SK patients with 54 skin lesions were enlisted, which were separated into three groups. The first group received topical 5-FU twice daily, the second group received one 10-second freeze-thaw cycle of liquid nitrogen cryosurgery, and the third group received topical calcipotriol twice daily. The success of therapy was assessed based on the reduction in baseline lesion size, and observations were made every two weeks for three months. **Result:** This study found that at the 12th week, the mean percentage of decrease in lesion size in group I was 34.6%, group II was 100%, and group III was 6.18%. Statistically, there was a significant difference in the decrease in lesion size in groups treated with cryosurgery (p value<0.001). The most common side effect in group I was discomfort, whereas in group II it was hyperpigmentation. Patients from group III reported no negative effects. **Conclusion:** Topical 5-FU and topical calcipotriol are less effective than cryosurgery in SK in terms of reducing lesion size. However, topical 5-FU reduced the size of lesions more than topical calcipotriol.

Keywords: Cryosurgery, seborrheic keratosis, topical 5-fluorouracil, topical calcipotriol.

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| Article info |
Submited: 11-04-2025, Accepted: 08-07-2025, Published: 30-11-2025

BACKGROUND

Seborrhoeic keratosis (SK) is a benign tumour made up of epidermal keratinocytes. It is commonly pigmented and most common in the elderly. Seborrhoeic keratosis are normally asymptomatic; however they can be pruritic or produce irritation. The primary care of SK is the excision of lesions that can be treated with surgery and medicines. Several surgical methods can be used, including cryosurgery, curettage, electrodesiccation, electrocautery, excisions, shave excisions, and ablative and non-ablative lasers.[1] Data on the incidence of SK in Indonesia has never been reported. Based on data from the outpatient unit of the Department of Dermatology and Venereology, Dr. Hasan Sadikin Hospital, Bandung, from January 1, 2014, to December 31, 2016, there were 106 new cases of SK. Based on the data, cases of SK in women were found at 83% and in men at 17%. SK is most commonly found in the age group of 50-59 years at 31.13% and the age group of 40-49 years at 22.64%.

The most common reason for SK therapy is cosmetic.[2] One of the indications for SK therapy is persistent mechanical irritation resulting in inflammation, bleeding, and itching.[3] The aim of SK care is to eradicate lesions, which can be accomplished in a variety of ways, including surgery and medicines. Surgical treatments for SK include freeze surgery, curettage, electrodesiccation, electrocauterization,

DOI : 10.20473/bikk.V37.3.2025.172-178

surgical excision, shave excision, and ablative or non-ablative laser therapy. The Food and Drug Administration has only approved 40% hydrogen peroxide for SK therapy.[4] However, patients' desire to treat SK lesions with topical therapy is growing,[5] therefore numerous topical therapeutic modalities are being developed and studied further.[4] Cryosurgery using liquid nitrogen is the conventional treatment for SK. The success of cryosurgery is dependent on the thickness of the SK, the freeze time, and the number of freeze-thraw cycles.[1] Scarring, hypopigmentation, and recurrence are among the potential complications.

This study seeks alternatives to cryosurgery. Oral 1,25-dihydroxyvitamin D3 has been found to be beneficial in the treatment of SK. Calcipotrienes' effect on keratinocyte growth may benefit SK.[6,7] A variety of epidermal malignancies, including basal cell epithelioma, actinic keratosis, Bowen's disease, squamous cell carcinoma, and psoriasis, have been proven to respond favorably to a 5-fluorouracil (FU) cream. However, no investigators have reported utilising it for SK. In SK, the 5-FU cream preferentially destroys aberrant keratinocytes, causing erosion or ulceration, but it does not harm normal keratinocytes surrounding the lesions.[8,9] This study investigated the comparison of the effectiveness of topical 5-FU, topical calcipotriol, and liquid nitrogen cryosurgery in SK. In this study, the reduction in lesion size indicates the effectiveness of the therapy.

METHODS

Patients with SK who visited the Dermatology Clinic of Dr. Hasan Sadikin Hospital from December of 2017 to April of 2018 were the candidates for this study. We enrolled 54 SK lesions, three lesions from each of 18 patients, and divided them into three groups. All patients were fully informed about their treatment and provide written informed consent. Group I was treated with topical 5-FU twice daily, group II was treated with one 10-second freeze-thaw cycle of cryosurgery, and group III was treated with topical calcipotriol twice daily. The effectiveness of therapy was assessed every two weeks for three months. Patients documented their daily applications in a log to verify compliance with the study procedure.

Lesions on the face, chest, lower arms, and hands were treated. The chosen lesion sizes ranged from 3 mm to 10 mm. Before treatment, each lesion was photographed, its diameter was measured, and the circumference was then outlined with wax paper. To calculate the area affected over time, the diameter of the lesions was measured, and the shape of each lesion was traced. At each weekly appointment, the diameter and circumference were measured. Adverse cutaneous reactions were documented and communicated to the institutional review board. The presence of scarring and/or pigment modification, as well as clinical signs of residual SK, was determined at the conclusion of the trial. This study defined improvement clinically. Clinical improvement indicated that the lesion would be replaced by normal-looking skin. The lesion's physical existence at the end of the study was judged to have no improvement. The researcher has received research approval from Dr. Hasan Sadikin General Hospital and a certificate of ethical feasibility from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung with the registry number LB.0401/AO5/EC/319/XI/2017.

Prior to statistical analysis, numerical data were tested for normality using the Kolmogorov-Smirnov test. Depending on data distribution, independent t-tests or Mann-Whitney tests were used to compare two groups. Repeated measures ANOVA or Friedman tests, were applied to assess differences in mean percentage reduction of lesion size among the three groups. Categorical data were analysed using the chi-square test, with Fisher's exact or Kolmogorov-Smirnov tests as alternatives when assumptions were not met. A p-value ≤ 0.05 was considered statistically significant. Data was processed using SPSS version 24.0 for Windows.

RESULT

The study included 18 participants, consisting of 13 males and 5 females, aged between 43 and 78 years. The majority were in the 60–69 age group (8 participants). A family history of SK was reported by 11 participants (61.1%). Regarding sun exposure, 10 participants (55.6%) had <3 hours/day, 3 participants (16.7%) had 3–6 hours/day, and 5 participants (27.8%) had >6 hours/day—all of whom were male.

As shown in Table 2, lesion distribution was similar across Groups I, II, and III. The most common site was the face (50 out of 54 SK lesions), followed by the hand (2 lesions), chest (1 lesion), and arm (1 lesion).

Table 1. Research Participant Characteristics

Individual Characteristics	Total (n=18)
Gender	
Men	13
Women	5
Age	
40-49 years	1
50-59 years	2
60-69 years	8
70-79 years	7
Family history	
Yes	11
No	4
Unknown	3
Sunlight exposure history	
Less than 3 hours/day	10
3-6 hours/day	3
More than 6 hours/day	5

Table 2. Lesion Location

Location	Group			Total (n=54)
	I (n=18)	II (n=18)	III (n=18)	
Face	16 (88.9%)	17 (94.4%)	17 (94.4%)	50 (92.6%)
Hand	1 (5.6%)	1 (5.6%)	-	2 (3.7%)
Arm	1 (5.6%)	-	-	1 (1.9%)
Chest	-	-	1 (5.6%)	1 (1.9%)

Table 3. Percentage of decrease in tumour size

Variable	Group			P-value
	I (n=18)	II (n=18)	III (n=18)	
The mean percentage reduction in lesion size after 12 weeks of therapy				<0,001**
Mean±SD	34.06%±31.297	100%	6.18%±11.486	
Median	21.49%	100%	1.72%	
Range(min-max)	2.00%-100.0%	100%	0.00%-38.09%	

SD = Standard deviation

From 18 patients assessed for entering the trial, including 13 males and 5 females, all patients were included and completed the course of treatment successfully. The mean baseline tumour size was 6.49±1.620 millimeter (mm) (group I) (Figure 1), 6.07±0.980 mm (group II), and 5.85±0.754 mm (group III). The mean improvement percentage was 34.06%±31.297 (group I), 100% (group II), and 6.18%±11.486 (group III), respectively, with a significant difference between them ($p<0.001$). At week 12, SK lesions that responded very well to topical 5-FU therapy were found in a few lesions; the group treated with topical calcipotriol did not have a very satisfactory response, while the group treated with freeze surgery had a very satisfactory response in all SK lesions. Table 3 provides further details.

Post-inflammatory hyperpigmentation (PIH) was observed in 19 lesions across groups. The most frequent adverse effect in Group I was irritation, while Group II showed the highest incidence of hyperpigmentation. Notably, no adverse effects were reported in Group III.

Table 4. Side Effects of Topical 5-Fluorouracil, Cryosurgery, and Topical Calcipotriol in Seborrhoeic Keratosis

Side Effects	Group I	Group II	Group III
Irritation	10	-	-
Allergic contact dermatitis	-	-	-
Hypopigmentation	8	3	-
Hyperpigmentation	9	10	-
Pain	-	3	-
Photosensitivity	-	-	-
Oedema	-	-	-
Urticaria	-	-	-
Bullae	-	-	-
Depigmentation	-	-	-
Atrophic scarring	-	-	-
No adverse effect	-	-	18

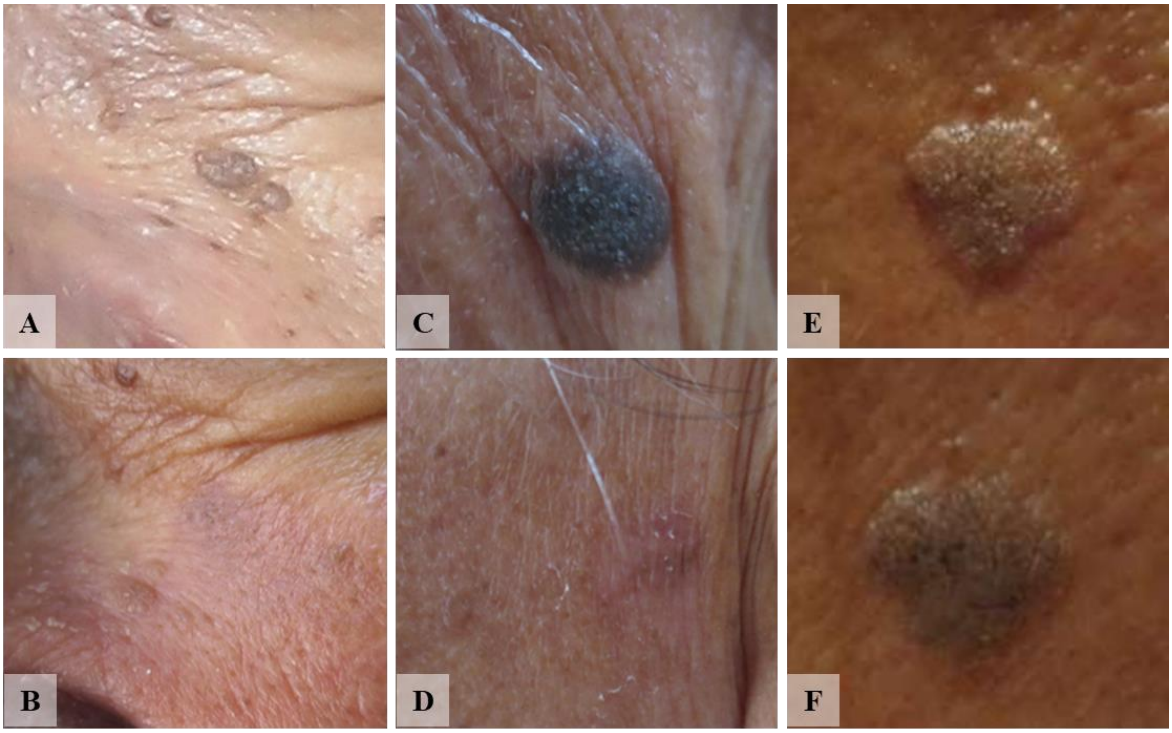

Figure 1. Clinical images of seborrhoeic keratosis lesions on the face before and after treatment. A 65-year-old man with seborrhoeic keratosis before treatment **(A)** and after 12 weeks of topical 5-fluorouracil application **(B)**. A 75-year-old man with seborrhoeic keratosis before treatment **(C)** and after 12 weeks of cryosurgery **(D)**. A 72-year-old man with seborrhoeic keratosis before treatment **(E)** and after 12 weeks of topical calcipotriol application **(F)**.

DISCUSSION

In this study, the majority of participants were male (13 out of 18), which aligns with previous findings by Luo et al., who reported a higher incidence of SK in males (1.3:1 ratio) in a large cohort. Although epidemiological studies generally suggest no significant sex-related differences in SK prevalence, the male predominance observed here may be explained by occupational or lifestyle-related sun exposure. This supports the theory that cumulative ultraviolet radiation is a key contributing factor to SK pathogenesis. Consistent with Luo et al., who demonstrate male with lesions predominantly located in sun-exposed head, neck, chest, and back regions.[10]

Heidenreich et al. further reported a correlation between cumulative UV exposure and FGFR3 mutations, which play a role in the molecular pathogenesis of facial and cervical SK.[11,12]

Age distribution in this study showed the highest frequency of SK in participants aged 60–69 years (8/18), corroborating findings from Nair et al., who found lesions mostly in the age range from 51 to 70 years.[13] Lesion distribution was also consistent with previous literature, with the face being the most frequently affected site (50 out of 54 lesions), likely due to its constant sun exposure. Other sites included the dorsal hand, chest, and forearm. This anatomical pattern reinforces the role of UV radiation in SK development.[10]

Interestingly, 11 participants reported a positive family history of SK, suggesting a possible genetic predisposition. Previous studies have proposed an autosomal dominant inheritance pattern, particularly in cases involving multiple lesions and early onset. In support of this, two participants in our study were siblings, both presenting with multiple lesions.[13]

There are no therapy guidelines for determining the appropriate freezing time and procedure for eliminating SK lesions.[14] Flat SK lesions typically require one freeze-thawing cycle lasting 5-10 seconds, whereas thick lesions require a longer freezing duration, two freeze-thawing cycles, and, in some cases, more than one therapy session until the lesion cures.[11,14,15] In this study, SK underwent a single freeze-thaw cycle for 10 seconds using an open spray technique with liquid nitrogen. All of the SK treated with cryosurgery showed clinical and histological improvement, and after one session, the SK showed oedema, blister formation, crusting, erosion, and complete reepithelialisation at one month. The number of cryosurgery sessions required to achieve complete resolution ranged from one to three, with two-week intervals.[1] Different results were reported by Herron et al.,[16] who mentioned that the cure rate of SK treated with freezing surgery at week 4 observation was 100%.

5-Fluorouracil is an antimetabolite drug that interferes with cell metabolism and the cell cycle. Its primary mechanism is the inhibition of thymidylate synthase, an enzyme essential for DNA synthesis, and disruption of RNA synthesis during the S phase.[17] After cellular uptake via the same transport pathway as uracil, 5-FU is converted into several active metabolites—FUMP, FUTP, FdUTP, and FdUMP—through multiple enzymatic pathways.[18-20] These metabolites exert cytotoxic effects by inhibiting thymidylate synthase and interfering with RNA synthesis, ultimately leading to impaired DNA/RNA function and cell death. Therefore, 5-FU can be considered a therapeutic option for treating SK.[21,22] There was only a single case of SK that was treated with topical 5-FU. Natarelli et al. described one case of large SK on the scalp with hair, which was treated with topical 5-FU and occlusion for three weeks. At the six month observation, there was complete healing, normal-looking skin, and no alopecia. The effectiveness of topical 5-FU in SK lesions has never been studied.[6]

Calcipotriol is a synthetic analogue of vitamin D3 (1,25-dihydroxyvitamin D3) with anti-inflammatory and antiproliferative properties.[23,24] Through binding to the vitamin D receptor (VDR), a nuclear receptor expressed in keratinocytes, melanocytes, mast cells, and lymphocytes, it regulates cell growth, differentiation, immune function, and apoptosis. Calcipotriol-VDR complexes form heterodimers with retinoid X receptors (RXR) and modulate gene expression via vitamin D response elements (VDREs).[25-27] Vitamin D3 and its analogue inhibit keratinocyte proliferation, promote terminal differentiation, and exhibit antitumor effects by inducing apoptosis and modulating growth factor receptor expression. The therapeutic effect of calcipotriol on SK lesions is primarily through apoptosis induction in keratinocytes.[25,27] Herron et al. found no significant decrease in lesion size in the group treated with calcipotriol ointment 0.005% for 16 weeks.[16] Patel et al. reported 35.3% patients that received calcipotriol had a >80% decrease in the number of SK lesions whereas 50% patients had a decrease between 40-80%. Only 14.7% had a <40% decrease in the number of SK lesions.[5]

The efficacy of 5-FU is linked to early discomfort within one month, which normally improves with further treatment. The use of 5-FU cream resulted in clinical remission in two patients after the study. When patients request topical treatment, 5-FU cream taken twice daily can result in clinical remission of SK.[14,28-30] Several factors can affect efficacy in this study, such as patient compliance in applying topical drugs twice a day for 12 weeks and differences in the distance of spraying the open spray technique on each SK lesion.

In our investigation, calcipotriol had no therapeutic benefit in reducing the size of SK. Herron et al. conducted a study in which routine cryosurgery was compared to many topical medicines, including calcipotriol. They found no clinical improvement with calcipotriol 0.005% ointment once or twice daily, which is consistent with our findings.[16]

In Group topical 5-FU, the most common adverse effects were irritation (10/18 SK lesions), hyperpigmentation (9/18), and hypopigmentation (8/18), which are consistent with known side effects of topical 5-FU.[20,21] Skin irritation typically appears between days 5–10 on the face and days 10–14 on the trunk and extremities. In this study, irritation occurred in week 2 (6 lesions) and week 4 (4 lesions). In cryosurgery group, hyperpigmentation (10/18), pain (3/18), and hypopigmentation (3/18) were the main adverse events. In calcipotriol group, no irritation or burning was observed, supporting previous findings by Herron et al. that topical calcipotriol is safe with minimal side effects in SK treatment.[16] Although cryosurgery is generally safe, pigmentary changes are more common in patients with darker skin and may be irreversible. Findings were consistent with Gurel et al., who reported hyperpigmentation as the most frequent side effect, while Jackson et al. noted more hypopigmentation in follow-up at 2 and 4 months.[14,31,32] Pain from cryosurgery was generally well tolerated; only three participants reported moderate pain (score 5–6), which resolved within hours. Painful lesions were located on the temples and postauricular area, in line with known anatomical variations in pain sensitivity.[33]

The limitation of this study is that several studies on SK therapy conducted longer observations of up to one year to assess the effectiveness of topical therapy and recurrence after therapy. This study involved a 12-week observation period, which limited the assessment of the effectiveness of topical therapy and the recurrence rate.

In conclusion, cryosurgery showed superior efficacy in reducing SK lesion size compared to topical 5-FU and calcipotriol. By week 12, all lesions treated with cryotherapy had excellent responses, while only a few in the 5-FU group responded similarly, and none in the calcipotriol group. Among topical treatments, 5-FU was more effective than calcipotriol. Adverse effects were most common with cryotherapy (hyperpigmentation, hypopigmentation, pain) and 5-FU (irritation, burning, hyperpigmentation), while calcipotriol was well tolerated. These findings support cryosurgery as the most effective option for SK, with 5-FU as a potential alternative. Further studies are recommended to assess the long-term outcomes of topical treatments, the impact of an occlusive 5-FU application, and optimisation of cryotherapy techniques.

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