

The Efficacy, Safety and Tolerability of Sulfur in the Treatment of Scabies: A Cross-Sectional Study

Skabiyez Tedavisinde Sülfürün Etkinliği, Güvenirliği ve Tolerabilitesi: Kesitsel Araştırma

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ABSTRACT Objective: The incidence of scabies has been increasing. The emergence of cases non-responsive to permethrin has urged the need for alternative treatments. Although sulfur has been considered an option for scabies treatment, there has been no conclusive data on this topic. The study was conducted to determine the efficacy and safety of sulfur in scabies. **Material and Methods:** All scabies patients treated with topical sulfur from January 2020 to February 2022 were included in the study. Procedurally, 5-10% sulfur was applied on three consecutive days and washed off every 24 hours (the duration varied depending on the patient-related factors or clinician's experience). The treatment was repeated if there was no cure at control. **Results:** There were 64 (39 female) patients. After 3-day treatment, 72% were cured. The overall cure rate was 92%. The median duration of therapy was three days (2-30). The length of treatment was correlated with the duration of pruritus before diagnosis and was longer in patients with widespread lesions. The side effects were more severe in those with extended lesions and those with more prolonged treatment. **Conclusion:** The present study demonstrates that sulfur is effective in majority of the patients after 3-day treatment. Most patients had no or minimal side effects. As the side effects increase with the length of treatment, the additional application should be reserved for those who are not cured at the control visit. Particular attention should be given to patients with widespread lesions since they require prolonged treatment and have an increased risk of side effects.

ÖZET Amaç: Skabiyez (uyuz) insidansı giderek artmaktadır. Permetrin yanıt vermeyen vakaların ortaya çıkması alternatif tedavilere ihtiyaç duyulmasına neden olmuştur. Sülfür (kükürt), skabiyez tedavisinde bir seçenek olarak görülse de bu konuda net bir veri bulunmamaktadır. Bu çalışmada, skabiyez tedavisinde sülfürün etkinliğinin ve güvenirliliğinin belirlenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışmaya Ocak 2020-Şubat 2022 tarihleri arasında topikal sülfür ile tedavi edilen tüm skabiyez hastaları dâhil edildi. Standart prosedür olarak %5-10'luk sülfür art arda 3 gün verildi ve her 24 saatte 1 yıkandı (tedavi süresi, hasta-ilişkili faktörlere veya klinisyenin deneyimine bağlı olarak değişmekteydi). Kontrolde iyileşmeyen hastalara tedavi tekrarlandı. **Bulgular:** Çalışmada 64 (39 kadın) hasta vardı. Üç günlük tedaviden sonra %72 hasta kür olmuştu. Toplamda kür oranı %92 idi. Ortanca tedavi süresi 3 gündü (2-30). Tedavi süresi tanı öncesi kaşıntı süresi ile koreleydi ve yaygın lezyonu olan hastalarda daha uzundu. Yaygın lezyonları olan ve daha uzun süre tedavi alan hastalarda yan etkiler daha şiddetliydi. **Sonuç:** Bu çalışma, topikal sülfürün 3 günlük tedaviden sonra hastaların önemli bir kısmında etkili olduğunu göstermektedir. Çoğu hastada yan etki yoktu veya hafifti. Tedavi süresi uzadıkça yan etkiler arttığından ek uygulama kontrolde iyileşmeyen hastalara yapılmalıdır. Yaygın lezyonları olan hastalara uzun süre tedavi gerektiği ve artmış yan etki riski taşıdıkları için özel dikkat gösterilmelidir.

Keywords: Scabies; sulfur; therapy; drug resistance; permethrin

Anahtar Kelimeler: Skabiyez; sülfür; tedavi; ilaç direnci; permethrin

Scabies is a common parasitic infection caused by *Sarcoptes scabiei* var. *hominis*. It is highly contagious and causes significant morbidity worldwide. Recent reports from different geographic regions, including Türkiye, have indicated an abnormal increase in cases.^{1,2}

Topical permethrin 5% has been the drug of choice for scabies treatment and is conventionally applied once a week for 2 weeks.^{3,4} In recent years, an increasing number of cases that do not respond to topical permethrin and resistance to the drug have been mentioned.^{3,5} Moreover, it has been demonstrated that

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even though the treatment with permethrin is intensified, only around one-third of patients are cured at 3 weeks, and the time for cure may reach up to 2 months in some patients.^{3,6} Therefore, alternative anti-scabies treatments that are safe and accessible to patients are needed.

Topical sulfur in 5-10% concentration has been considered a cost-effective and safe treatment for scabies. However, there are limited data providing clear evidence on its effectiveness.⁴ Sulfur has not been ranked as one of the best options in scabies treatment, and the results of the studies have been contradictory.^{4,7-12} Additionally, many patients commonly encountered in daily practice, including pregnant women, children, immunosuppressed patients, and those with systemic illnesses, were excluded from the previous studies.¹⁰⁻¹² Last but not least, there has been no data on the effectiveness of sulfur in patients who do not respond to topical permethrin.

The current study aimed to investigate the effect of topical sulfur in the treatment of scabies in a real-life setting and to assess the outcome of treatment on permethrin-resistant cases.

MATERIAL AND METHODS

We retrospectively included all consecutive patients with scabies from January 2020 to February 2022 who were treated with topical sulfur. This study was approved by Başkent University Institutional Review Board (Project no: KA22/269) and supported by Başkent University Research Fund and performed in accordance with the principles in the Declaration of Helsinki.

SCABIES DIAGNOSIS

The diagnosis was made according to the following criteria: 1) Demonstration of mites, eggs, or fecal material by light microscopy in skin scrapings, 2) Identification of the characteristic burrow (tunnel) by dermoscopy (Figure 1), 3) The presence of the typical lesions at the sites of predilection (Figure 2), intense pruritus, particularly worsening at night, and a history of similar symptoms in the family and/or close contacts.



FIGURE 1: Dermoscopic image of a burrow revealing "jet trail" and "delta" (head of mite) signs.



FIGURE 2: A characteristic linear keratotic lesion (burrow) on the dorsum of finger.

THE TREATMENT PROTOCOL

For about 2 years, the sulfur treatment protocol we have been applying in our clinic is 5-10% precipitated sulfur in petroleum given for 3 successive days. In patients with a high number of tunnels, we may choose to prolong the duration of treatment. In past years, we used to advocate longer treatments, but since shorter treatments have also started to be recommended, we have started giving 3-day treatments

for a while. The drug is procedurally applied all over the body from neck to toe and washed off after 24 hours. For infants, we recommend applying the drug to the face and scalp as well. The application is repeated throughout the treatment period (a bath is taken between each application). Patients are routinely given an information sheet explaining how to use the drug in detail, the importance of simultaneous use of the drug by the family and close contacts, and how to decontaminate their clothes, belongings, and households. According to our protocol in the present study, 10-14 days after the end of the 3-day treatment, we examined the patients clinically in detail, and the treatment was repeated if there was no cure.

DATA COLLECTED

The data collected were as follows: age and gender of the patient, associated diseases, suspected source (inside the home, outside the home, no known source), the presence of household with pruritus (yes, no, living alone), the duration of the pruritus (weeks), the severity of pruritus (mild, severe), the timing of pruritus (worsening at night/waking up from sleeping, also present in the day, worsening in the morning), the severity of secondary lesions (mild: few scattered excoriations and papules or nodules over the torso and extremities, severe: widespread excoriations and papules or nodules over the torso and extremities, or prominent lichenified plaques), the number of burrows (1-2, more than 2, no visible burrow), prior treatment for disease other than scabies (received, not received), the type of treatment for disease other than scabies (oral antihistamines, topical antihistamines, topical steroids, and others), previous treatment for scabies (received, not received), the type of previous scabies treatment (topical permethrin, commercially available sulfur containing ointment (12.5%), magistral drugs, and others), the application of previous scabies treatment (applied as recommended, long-term and/or repeated courses, incomplete/incorrectly treatment), the method of scabies diagnosis (burrows on dermoscopy, demonstration of mites, eggs or scabala on light microscopy, clinical diagnosis), the percent of sulfur (5%, 10%), the duration of sulfur treatment (days), the accuracy of sulfur treatment ap-

plication (yes, no), the result of sulfur treatment (cure, not cure), side effects of the sulfur treatment (no side effect/mild xerosis, severe xerosis/contact dermatitis), the duration of the second sulfur treatment (days), the result of second sulfur treatment. In addition, all the treatments were recorded in patients who received more than one type of non-scabies or scabies treatment.

STATISTICAL ANALYSIS

Statistical analyses were performed using Statistical analyses were performed using SPSS software v25.0 (IBM Corp., Armonk, NY, USA). The chi-square and Fisher tests were used for categorical data. For data involving numeric variables, the Mann-Whitney U test was used for the comparisons of 2 groups, whereas Kruskal-Wallis test was used for the comparison of 3 or more groups. Spearman correlation was performed to determine the correlation between categorical or quantitative variables not normally distributed. A p value less than 0.05 was considered significant.

RESULTS

The demographic and clinical characteristics of the patients are given in [Table 1](#). There was no crusted scabies (Norwegian) case. The data on the diagnosis and the treatment of patients are given in [Table 2](#). The treatment response and the duration of treatment (days) were not statistically different according to the presence or absence of immunosuppression, the number of burrows, the previous use of topical steroids, and the previous scabies treatment status.

Although there was a negative relationship between the duration of pruritus and the likelihood of a response to treatment, it did not reach a statistically significant level ($p=0.055$, $r=-0.241$). On the other hand, there was a significant positive relationship between the duration of pruritus and the length of treatment ($p=0.004$, $r=0.371$). The severity of secondary lesions did not affect the likelihood of response; however, the duration of treatment was significantly longer in patients with widespread lesions ($p=0.043$). In addition, the side effects were significantly more severe in those with extended secondary lesions

TABLE 1: Demographic and clinical data of the patients with scabies treated with sulfur.

Age (years) mean±SD/median (minimum-maximum)	37±21/28 (2-84)
The duration of the pruritus (weeks) mean±SD/median (minimum-maximum)	11±8/10 (1-32)
Gender n (%)	
Male	25 (39.1)
Female	39 (60.9)
The presence of associated disease n (%)	
Present	18 (28.1)
Absent	46 (71.9)
Immunosuppressive treatment n (%)	
Present	4 (6.3)
Absent	60 (93.8)
Suspected source n (%)	
In the house	9 (14.1)
From outside the house	33 (51.6)
Unknown	22 (34.4)
The presence of household with pruritus n (%)	
Yes	32 (50)
No	26 (40.6)
Living alone	5 (7.8)
Unknown	1 (1.6)
The severity of pruritus n (%)	
Severe	54 (85.7)
Mild	9 (14.3)
The type of pruritus n (%)	
Also during the day	3 (4.7)
Increasing in the evening/waking in the night	58 (90.6)
Wakes up in the morning	2 (3.1)
The extent of secondary lesions n (%)	
Mild	29 (45.3)
Severe	35 (54.7)
The number of burrows n (%)	
1-2 burrows	41 (64.1)
>2 burrows	17 (26.6)
Could not seen	6 (9.4)
Previous treatment other than scabies n (%)	
Received	34 (53.1)
Not received	29 (45.3)
Unknown	1 (1.6)
The type of treatment for diseases other than scabies n (%)	
Oral antihistamines	5 (7.8)
Topical steroids	2 (3.1)
Oral antihistamines+topical steroids	12 (18.8)
Oral+topical antihistamines	2 (3.1)
>3 drugs	5 (7.8)
Unknown	8 (12.5)
Previous treatment for scabies n (%)	
Received	32 (50)
Not received	31 (48.4)
Unknown	1 (1.6)
The type of previous scabies treatment n (%)	
Topical permethrin	24 (37.5)
Commercially available sulfur pomade (12.5%)	1 (1.6)
Magistral drug	1 (1.6)
>1 type of drug	5 (7.8)
Herbal mixtures	1 (1.6)
The application of previous scabies treatment n (%)	
Recommended/appropriate application	17 (26.6)
Longer than recommended/multipl repeated courses	9 (14.1)
Incomplete/incorrect application	6 (9.4)

SD: Standard deviation.

($p=0.020$) and those with a longer duration of treatment ($p=0.004$, $r=0.315$).

DISCUSSION

The increase of permethrin-resistant scabies patients in recent years has prompted the need for alternative treatments.³ Topical sulfur has been considered a safe treatment for scabies. Although its ovicidal activity seems to be advantageous, there is still no clear evidence on the effectiveness of sulfur in the treatment of scabies.⁴ While there are reports indicating that sulfur is inferior to other options, others demonstrated

TABLE 2: Data on the diagnosis and treatment characteristics of scabies patients with sulfur.

The method of scabies diagnosis n (%)	
Burrow on dermoscopy	25 (39.1)
Sarcoptes on KOH examination	31 (48.4)
Eggs/scybala on KOH examination	1 (1.6)
Clinical diagnosis	7 (10.9)
The percent of sulfur n (%)	
10%	62 (96.9)
5%	2 (3.1)
The duration of 1 st sulfur treatment (days) mean±SD/median (minimum-maximum)	3.94±3.7/3 (2-30) ^a
The accuracy of sulfur application n (%)	
Correct application	59 (92.2)
Incorrect application	5 (7.8)
The result of 1 st course sulfur treatment n (%)	
Cure	46 (71.9%)
Scabies persists	13 (20.3%)
Additional scabies treatment in other clinic	5 (7.8%)
Side effect of the sulfur treatment n (%)	
None/mild xerosis	49 (76.6)
Moderate to severe xerosis/eczema	14 (21.9)
Other	1 (1.6)
The duration of 2 nd sulfur treatment (n=13) ^b mean±SD/median (minimum-maximum)	2.77±0.43/3 (2-3)
The result of 2 nd sulfur treatment (n=13) ^b n (%)	
Cure	13 (100)
Scabies persists	0 (0)
Additional scabies treatment in other clinic	0 (0)
Total duration of sulfur treatment (days) mean±SD/median (minimum-maximum)	4.53±3.87/3 (2-30) ^a
The end result of sulfur treatment n (%)	
Cure	59 (92.2)
Not cure	5 (7.8)

^aOne patient was unable to admit control visit on time, and it was found out that he had applied sulfur for 30 days despite the instructions; ^bThe second course of treatment was applied to 13 patients; KOH: Potassium hydroxide.

that it is very effective in scabies.^{7-10,12} The differences in the concentrations of sulfur formulations and the treatment schemes among the studies make it difficult to establish a standard protocol to achieve a cure.^{7-9,13,14}

The studies favoring sulfur reported cure rates between 71% and 100%. The sulfur concentration ranged from 2% to 10% in these studies. In some studies, the drug was left overnight, whereas in others, it was kept on the body for 24 hours (Table 3).

In our cohort, the overall cure rate was 92.2%. With the first course of treatment, 72% of patients were cured, while the rest required a second course of application. Of those who were cured at the first course, 83% received a 3-day treatment. There was no patient who received the second course of treatment and could not be cured. The median duration of total treatment was 3 days (2-30). One patient could not attend to control visit due to the operation of the sarcoma on his leg, and despite the instructions, it was learned that he incorrectly applied the drug for 30 consecutive days. He was eventually cured but had severe contact dermatitis. It must be noted that we considered the patients who received scabies treatment in another center after our treatment due to the persistent itching as “not cured”. As might be expected, these patients may have been suffering from post-scabies pruritus. If so, our success rate with sulfur treatment may be higher.

It is difficult to compare and interpret the results of studies that report poor response to sulfur treatment.^{10-12,15} Many factors, including low concentrations, leaving the drug only overnight, or the duration of application, might be suggested to result in low response rates. However, the treatment schemes and durations were similar between the studies where sulfur was effective, and not effective.⁷⁻¹⁵

One of the reasons we found sulfur highly effective may be that we gave all patients a detailed written instruction form. It is well known that improper application of the drug, the lack of simultaneous treatment of close contacts, and improper disinfection of household items can lead to treatment failure.¹⁴ It is not indicated whether detailed information was given to patients in studies where sulfur did not work.^{10,11,15} The fact that Mila-Kierzenkowska et al. provided detailed instructions but did not find 10% sulfur effective in any of the 18 patients at the end of one week indicates that other factors play in the failure of the treatment.¹² This discrepancy brings into question the resistance across different geographic regions.

Sulfur has been considered a safe treatment for pediatric patients and used in different concentrations (2-10%) according to age (range, 2 months-12 years) in pediatric patients.^{4,7,8,13,14} There were 5 pediatric patients aged between 2-6 years in our cohort. For the patients 2 years and under, we used 5% sulfur,

TABLE 3: The data of the current studies favoring sulfur treatment in scabies.

Author, year, reference number	Sulfur percent	Number of patients	Treatment schemes ^a	The response rate
Sharquie et al., 2012, ^{b,9}	8-10%	A: 33	A: 1 day (24 hours)	A: 42.4%
		B: 32	B: 3 consecutive nights (bathing every day)	B: 90.6%
		C: 32	C: 3 consecutive days (bathing every 24 hours)	C: 96.9%
Diaz et al., 2004, ⁷	2-8%	40	Applied for 6 consecutive days (left overnight and then washed off except for children under <2 years old), and after a 1-week rest, repeated for another 2 days	95%
Cazorla et al., 2006, ⁸	2.5%	71	Left for 8 hours for 2 days, and re-applied 2 days after 2-weeks rest	100%
Singalavanija et al., 2003, ¹³	10%	37	7 consecutive nights	83%
Pruksachatkunakorn et al., 2002, ¹⁴	5/10%	102	3 consecutive days, repeated 1 week later (four applications in total)	71%

^aThe treatment schemes are denoted as indicated in the corresponding articles; ^bThe patients treated with sulfur were divided into three groups.

whereas the older children received 10%. There is evidence that 10% sulfur could also be used in patients older than 6 months.¹³ Considering pregnant women, sulfur has also been considered a safe treatment.⁴ We had only one pregnant patient, and after a 3-day treatment with 10% sulfur, the patient and her family, who had been itching for months, were cured.

A strength of the study is that the diagnosis of scabies was made by the microscopic examination or dermoscopy in most of the patients. Additionally, our real-life study design includes a wide range of patients, contributing to the generalization of the results and providing important information for daily clinical practice. In most of the studies mentioned above, deviating from real-life setting, individuals, including pregnant women, immunocompromised patients, patients with systemic illnesses, and patients who received prior scabies treatment or topical corticosteroids were excluded from the analyses. Having previous anti-scabies treatment did not affect the sulfur treatment response or duration. In the era where resistance to permethrin has been seen, the current study demonstrates that patients who can not be treated with permethrin can also be cured with sulfur. In a very recent study, the use of topical steroids before scabies diagnosis has been associated with resistance to therapy, where “having a treatment period of 28 days or longer” has been regarded as “treatment resistance”. All the patients in that study were cured (the maximum time to cure was 56 days) by the end of the study regardless of previous topical steroid use status.⁶ In our study, there was no difference in response to treatment or duration of treatment between patients who had previously used topical steroids and those who had not. Similarly, we have observed that sulfur was equally effective in both immunocompetent and immunosuppressed patients.

The most common side effect of sulfur treatment is skin dryness which is frequently mild and transient.^{10,12} Burning sensation, irritant contact dermatitis, and erythema are the other side effects.^{7,9,10,14,16} Midfacial edema has also been reported.¹⁴ Compatibly, 76% of our cohort had no side effects or suffered mild skin dryness, which was well tolerated. Twenty-two percent of the patients had severe xerosis or contact dermatitis. A two-year girl presented with edema

and erythema of the eyelids and urticarial plaques on the chest. Skin biopsies were performed on 2 patients with severe eczematous skin lesions and a two-year boy with recurrent itchy nodules. The histopathological examination of eczematous lesions and the nodule revealed a perivascular and interstitial infiltrate rich in eosinophils which were compatible with allergic contact dermatitis. They were managed with oral antihistamines, topical steroids, and in need, systemic steroids.

Sharquie et al. did not observe any difference between a single-day, 3 successive nights, and 3 consecutive days of administration of sulfur in terms of side effects.⁹ The risk of contact dermatitis was significantly related to the duration of sulfur therapy in our study. Accordingly, we suggest that it would be more reasonable to give the treatment for 3 days at the diagnosis and lengthen the treatment duration according to the result of the control visit. However, we suggest that the patients with widespread secondary lesions need close follow-up since the risk of side effects is higher and the duration of treatment is longer in these patients. According to our results, we can conclude that sulfur treatment may cure patients with long-term pruritus; but in a longer time. Therefore, early diagnosis is the key to rapid response. The correlation between the number of burrows and the severity of secondary lesions suggests that the extent of secondary lesions reflects the burden of mites. The fact that the duration of treatment was not related to the number of burrows but to the severity of secondary lesions suggests that the extent of secondary lesions negatively affects the treatment response regardless of the number of mites. Nevertheless, the categorization of the data and the sample size might have affected the results. Further studies are required to confirm this finding.

Besides providing insights into sulfur therapy, our study offers essential information about the clinical features, diagnosis, and follow-up of scabies. During control visits, asking for pruritus is not enough to rule out scabies, and a detailed dermatological examination is crucial. One of our patients was completely free of pruritus 10 days after the end of the 3-day treatment, however, potassium hydroxide examination of a keratotic lesion on her hand, a



FIGURE 3: Microscopic image of eggs in skin scrapings of a burrow remnant after 3-day sulfur treatment (10% potassium hydroxide mount).

remnant of an old burrow, revealed eggs of mites (Figure 3). Since there is no established method to determine whether the egg is alive or dead, we followed the patient for 2 days, and although she did not have pruritus, a second 3-day treatment was given.⁴ This patient may actually have been cured with the first treatment. Some of the patients with confirmed scabies had itching during the day and stated that the severity was not different from that at night, whereas

a few had mild pruritus without sleep disruption. Also, there were cases who had severe pruritus, but none of their family members had any symptoms. Therefore, in case of doubt, it is essential to perform a thorough examination, not to rely only on history. In the author's experience, establishing the diagnosis may require a 20-minute inspection in some patients. There was a patient with a delta sign in the dermoscopic examination of a punctate papule without an obvious jet trail sign (Figure 4). This finding emphasizes the importance of dermoscopy to visualize the mite itself before an apparent burrow is formed. Burrows may not be located on the sites where the pruritus is the most severe. The nodules on the genital region are highly characteristic but may also be located on other intertriginous regions (Figure 5). Even if no mite is left in the body, these lesions can sometimes flare-up.

An ideal treatment for scabies should be cost-effective, safe, ovicidal, easily accessible, and takes the patient's compliance into consideration. Unfortunately, there is no one anti-scabies treatment that fits all. It is controversial whether permethrin is ovicidal, however, it has been the first-line treatment to date.¹⁷ Oral ivermectin has been shown to be more effective than sulfur, but it is currently not available in Türkiye.¹¹ On the other hand, 10% sulfur is extemporaneously prepared in a pharmacy, which means the accessibility and quality depend on the pharmacist's experience. Its unpleasant smell and the fact

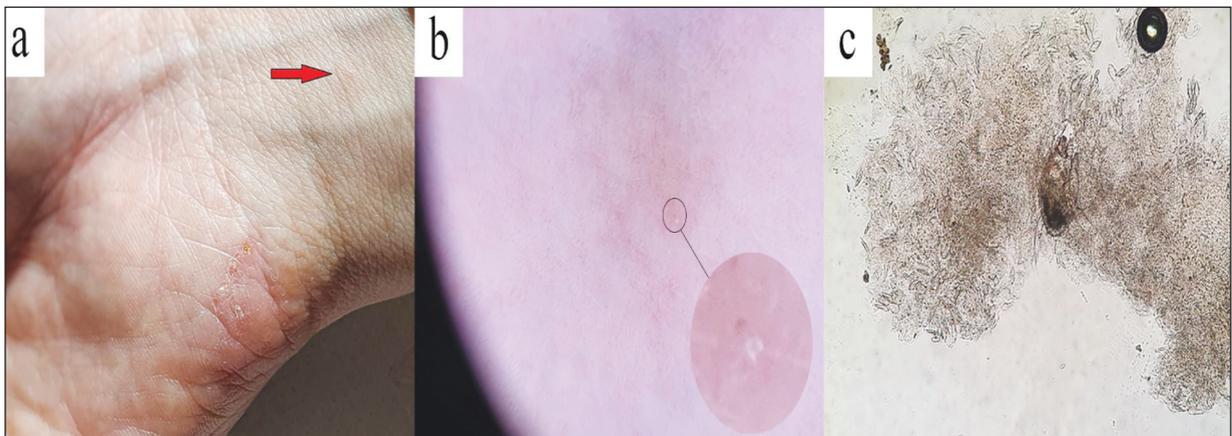


FIGURE 4: a) A punctate papule (red arrow) on the volar side of the right wrist, b) Dermoscopic image of delta sign without an apparent jet trail sign, c) The adult mite identified by microscopy (10% potassium hydroxide mount).



FIGURE 5: Itchy nodules on the right axilla of a two-year boy.

that not every patient is cured with a 3-day treatment are the other drawbacks. Nevertheless, it has been indicated as a cheap treatment.^{7,8,12}

CONCLUSION

In this real-life study, we provide a deep insight into the treatment of scabies with sulfur. Three-day treat-

ment is sufficient for a significant proportion of the patients. The patients who had previously received anti-scabies agents respond similarly to sulfur therapy, as do treatment-naïve patients. A detailed examination should be carried out in the control visit, and additional treatment should be given to patients who did not respond. Since the risk of side effects increases as the duration of treatment is prolonged, the length of treatment should be kept to a minimum. Additionally, the current study offers clinicians important information about the clinical characteristics, diagnosis, and follow-up of scabies patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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