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Adjunctive Agent for Treating Scabies: *In vitro* Killing Activity of Permethrin and Tea Tree Oil on *Sarcoptes scabiei* Collected from Patients

Skabiyes Tedavisinde Yardımcı Bir Ajan: Skabiyes Hastalarından Alınan Sarkoptes scabiei Paraziti Üzerinde Permetrin ve Çay Ağacı Yağının İn vitro Öldürme Aktivitesi

Aslan Yürekli

Kuşadası Public Hospital, Clinic of Dermatology, Aydın, Turkey

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ABSTRACT

Objective: Recently, there has been a serious increase in cases of scabies. The number of patients who do not benefit from the current treatment agents is also quite high. There are publications showing that scabies mites are permethrin-resistant and ivermectin. The treatment with scabicides usually lasts for several hours and usually the treatment is repeated for at least another time, which reduces the patient's compliance with the treatment, especially in pediatric patients where the toxic effects of the products are more pronounced. Therefore there is a need for treatment modalities that are less toxic to humans. To observe the *in vitro* effect of tea tree oil (TTO) on *S. scabiei* and to compare it with those of permethrin.

Methods: Scabies specimens were removed from the patient and examined using a digital microscope. Parasites that were not damaged during sampling, and showed full motion were included in the study. No treatment was applied to the patients before removal of the mites. A total of 40 parasites were included in the study, with 10 parasites in each group. Immersion oil was applied to the control group, 5% permethrin to the first treatment group, while 5% and 25% TTO were used for the second and third study groups.

Results: The mean survival time (ST) of scabies mites in the 5% permethrin group was 350±31.3 min, while this for 5% TTO group 180±15.1 min and 120±13.3 min in the 25% TTO group. The mean ST of the sarcoptes in the control group was 2.820±90 min. The mean ST between the control, permethrin and TTO groups was statistically significant (p=0.03). ST between 5% and 25% TTO groups was also statistically significant (p=0.04). There were no statistical differences between permethrin and 5% or 25% TTO.

Conclusion: TTO has an acaricidal effect on *S. scabiei*. Although not used as the treatment of choise, it can be used as a supportive agent. Since it shows an acaricidal effect within a short time, it could be used as a shampoo or shower gel to enhance the acaricidal activity of another scabicide.

Keywords: Scabies, tea tree oil, sarcopt

ÖZ

Amaç: Son zamanlarda uyuz olgularında ciddi bir artış görülmektedir. Mevcut tedavi ajanlarından fayda görmeyen hasta sayısı da oldukça fazladır. Çalışmalar, mevcut ajanlara direnç olmadığını ve tedavi etkisizliğinin tedaviye uyumsuzluktan kaynaklandığını ortaya koymaktadır. Tedavi ajanları uygulandıktan sonra en az sekiz saat vücutta kalmalı, herhangi bir şekilde vücuttan uzaklaştırıldıysa tekrar uygulanmalıdır. Elbette ki bu durum, hastanın tedaviye uyumunu azaltmaktadır. Özellikle çocuk hastalarda ilacı bu kadar uzun süre vücutta tutmak daha da zordur. Ana etkeni desteklemek için tedaviye uyumu artıran ve daha kısa süreli uygulama gerektiren tedavi modalitelerine ihtiyaç vardır. Bu çalışma, çay ağacı yağının *S. scabiei* üzerine etkisini *in vitro* gözlemlemek ve akarisit etkisinin olup olmadığını belirlemek amacıyla tasarlanmıştır.

Yöntemler: Uyuz hastalarından tanı amaçlı alınan örnekler dijital mikroskop kullanılarak incelendi. Örnekleme sırasında zarar görmemiş, parçalanmamış ve tam hareketli parazitler çalışmaya dahil edildi. Hastalara herhangi bir tedavi uygulanmadı. Hastalardan teşhis amaçlı alınan atık örnekler incelendi. Her grupta 10 parazit olmak üzere toplam 40 parazit çalışmaya dahil edildi. Kontrol grubuna immersiyon yağı; çalışma gruplarına %5 permetrin, %5 ve %25 çay ağacı yağı uygulandı.

Bulgular: Kontrol grubu (immersiyon yağı) dışındaki tüm çalışma solüsyonları *S. scabiei*'yi öldürdü. Ortalama sağkalım süresi (ST) %5 permetrin grubunda 350±31,3 dakika idi. Ortalama ST, %5 TTO grubunda 180±15,1 dakika, %25 TTO grubunda 120±13,3

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Address for Correspondence/Yazar Adresi: Aslan Yürekli, Kuşadası Public Hospital, Clinic of Dermatology, Aydın, Turkey
Phone/Tel: +90 543 414 66 46 **E-mail/E-Posta:** aslanyurekli03@hotmail.com **ORCID ID:** orcid.org/0000-0003-2812-2133

Türkiye PARAZİTOLOJİ Dergisi

dakika idi. Kontrol grubundaki sarkoptların ortalama ST'si 47±1,5 saat idi. Kontrol, permetrin ve TTO grubu arasındaki ortalama ST istatistiksel olarak anlamlıydı (p=0,03). %5 ve %25 TTO grupları arasındaki ST de istatistiksel olarak anlamlıydı (p=0,04).
Sonuç: Çay ağacı yağının sarkoptlar üzerinde akarisidal etkisi vardır. Ana tedavi ajanı olarak kullanılmasa da destekleyici ajan olarak kullanılabilir. Akarisidal etkisini kısa sürede gösterdiği için banyo sırasında şampuan, duş jeli vb. formların kullanılması ana tedavi maddesinin etkisini destekleyecektir.
Anahtar Kelimeler: Skabiyes, çay ağacı yağı, sarkopt

INTRODUCTION

Scabiosis is an ectoparasitosis caused by the *Sarcoptes scabiei var. hominis* and can affect everyone regardless of gender, age and race. Transmission from person to person occurs directly through sexual intercourse, communal life, close contact, or indirectly through the personal belongings of patients with scabies. Although the diagnosis can be made easily in most cases with the anamnesis and typical clinical findings, scabiosis may also appear with different clinical manifestations, e.g., scabies-in-the-clean, which can render diagnosis more difficult (1).

The most important step in being successful with the treatment is patient compliance. Sulfur-containing agents should remain on the body for 3 days, and permethrin-containing agents should remain on the body for at least 8 hours (2). Those agents should cover the entire body regions below the neck. In fact, when scalp involvement occurs in infants and children, these agents should also be applied to the scalp (3). The difficulty of treatment emerges at this stage. Patients either do not keep the drug in their body for as long as necessary or the drug is removed e.g., by hand washing. Unless an effective treatment is applied, reinfestations can occur and the disease becomes chronic among family members. Especially in infants and children, compliance with treatment becomes more difficult due to the reluctance of this age group to use topical drugs (4). The foreign body sensation created by the applied agents and the discomfort which creates in babies, can cause irritation and discomfort, especially in the diaper area, and the baby's constant hand in her mouth make the treatment in this age group more toxic. In our clinical practice, it is observed that the infestation tends to be more chronic in families with a baby or child. We think that treatment could last for shorter times and in order to increase it's efficacy is supported by addional agents.

"Tea tree oil" (TTO) is an essential oil which is being used in cosmetics and care products wordwide, and has become more popular in the last ten years due to its natural origin (5). TTO is accepted as an ideal disinfectant for topical use, as it has an antimicrobial effect against a wide range of microorganisms, penetrates the skin easily and does not cause irritation. Although the leaves of the tea tree have been used in traditional medicine for at least the 18th Century due to their antiseptic effect, It is thought to have been discovered by humans in the 1700s. The popular name of the plant, "tea tree", was first used for the leaves (possibly a *Leptospermum* species) that sailors took from this region to prepare tea on the return of Captain James Cook from his trip to Australia (1770). Today, plants belonging to *Leptospermum, Melaleuca* and *Kunzea* genera from Myrtaceae family are called "tea tree". The plants have no similarities with the real tea plant (*Camelia sinensis*) in terms of taste, smell and composition. The leaves of the plants in question carry an essential oil and all of these oils are known as "TTO" (6,7).

In our study, the scabicidal effect of TTO on *S. scabiei* was evaluated an compared to this of permethrin.

METHODS

Materials

Topical permethrin and TTO solution were obtained from the Jeomed Company (Turkey). A total of 40 parasites were included in the study, with 10 parasites in each group. Immersion oil was applied to the control group, while 5% permethrin, 5% and 25% TTO was applied to the three study groups.

Patients

The study was conducted in accordance with Helsinki Declaration principles. Ethical approval was obtained from İstanbul Medipol University (03/02/2022/73). For the trial, the authors used the material which was obtained for the diagnosis of scabiosis. The patients were not treated before the removal of the mites and the experiments were carried out on *Scabies* specimens *in vitro*. More than 300 samples were examined over a period of one year, however only 40 mites were suitable for the present study.

Design

Parasites that were not damaged during sampling and had full motions were included in the study, while immobile, partially mobile, fragmented, or surrounded by artifacts, were excluded from the study (Figure 1).

Specimens were collected with the help of dermoscopy, the location of the parasite was determined and the parasite was gently removed from the tunnel with the help of a 22 G needle (Figure 2). The samples were assessed by a digital

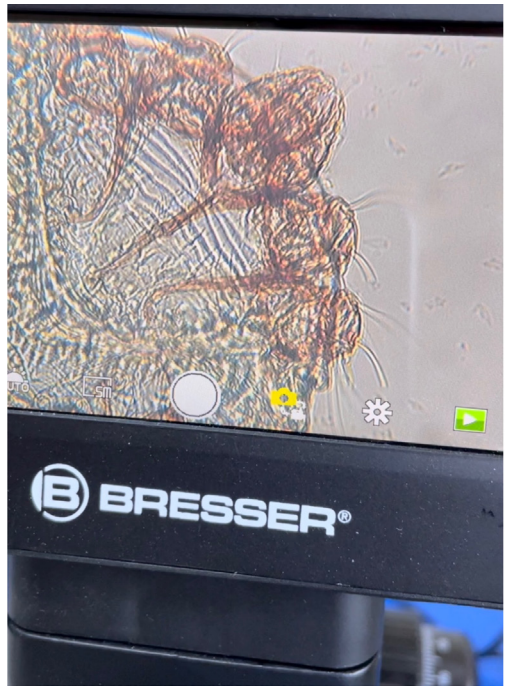

Figure 1. Parasite pattern without artifacts such as skin attachment blood etc.

Figure 2. *Sarcoptes scabie* parasite on a 22 G needle

microscope allowing magnification of 1600x (Bresser, LCD digital microscope) (Figure 3). A lamel was not used during the microscopic examination to protect the parasite as much as possible from external influences (Figure 4). A digital microscope was used to instantly monitor every movement of the parasite. Movements of parasites were checked every 60 minutes. IThe survival time (ST) was defined as the interval between the mites' first exposure to the solution to the time the movements ceased. The average ST was compared among different solutions to evaluate their *in vitro* killing activity. The experiments were carried at room temperature.

Figure 3. Bresser, LCD digital microscope

Figure 4. Lamel was not used during microscope examination

***In vitro* environment:** The parasite taken on the slide was examined on the digital microscope screen and it was determined whether it was mobile or not. Then, the working solutions were dripped onto this *in vitro* environment that was created on the slide (Figure 5). The moment of contact of the solution with the parasite could be monitored instantly through the screen of the digital microscope.

Statistical Analysis

Statistical analyses were performed using IBM SPSS (statistical package for social sciences) for Windows, Version 22.0 package program. Numerical variables were shown as mean ± standard

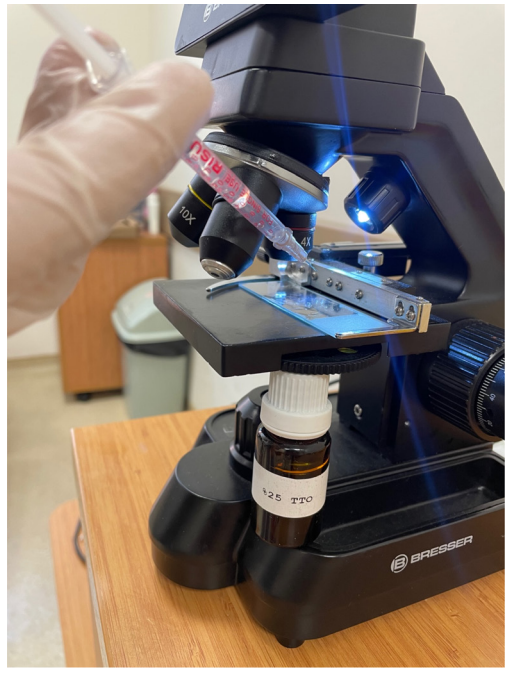

Figure 5. Method of application of the active substance

deviation. The data between groups were evaluated by a two-tailed t-test. P-value <0.05 was considered significant in all comparisons.

RESULTS

The mean ST in the 5% permethrin group was 350±31.3 minutes, while this of 5% TTO group 180±15.1 minutes and 120±13.3 minutes in 25% TTO group. The mean ST of the *Sarcoptes* in the control group was 2.820±90 minuntes. The mean ST between the control, permethrin and TTO groups was statistically significant (p=0.03). ST between the 5% and 25% TTO groups was statistically significant (p=0.04). There is no statistical differences between permethrin and 5% or 25% TTO (p>0.05).

DISCUSSION

Recently, there has been an increase in scabies cases both in our country and abroad (1). In our clinical practice, we frequently encounter chronic cases that did not respond to treatment. There are publications showing that Scabies mites are resistant to permethrin and ivermectin (8,9). Topical scabicides include permethrin, phenothrin, sulfur, benzyl benzoate, crotamiton, ivermectin, malathion, while as a systemic agent oral ivermectin is being used. Permethrin, a member of the pyrethroid family, contains pyrethrum components and derivatives. Permethrin 5% cream and lotion form shows scabicidal and ovicidal effects in the treatment of scabies (3).

Permethrin is recommended as the first treatment option in patients with uncomplicated classical scabies in many guidelines. The body should be dry and cool before topical application. It should be applied from the neck down, including between the fingers and other areas where no clinical signs were observed, and it should be washed after 8-12 hours. Especially in infants and adults with immune deficiency, this agent should be applied to the head area by protecting the eye and mouth area. Although it is recommended as a first-line treatment agent in infants older than three months, pregnant women and lactating women, care should be taken in terms of toxicity in individuals in this group, especially infants between 3-12 months, since less than 2% of the drug can enter the systemic circulation after a single application. Permethrin is the most effective scabicidal agent in clinical study meta-analyses in the literature. Treatment success rate of 89-98% after a single application reaches 98-100% after repeated application at 1 week interval (This sentence is not clear, please re-write!) (1-3), however lately studies show that scabies mites become resistance to permethrin (8,9).

TTO, which is considered a safe antiseptic due to its natural origin is being used in many pharmaceutical and cosmetic preparations in recent years, as it is effective on a wide range of microorganisms at very low concentrations (10,11). The main purpose of the scabicidal treatment is the contact of the agent with the parasite in the tunnel. Success for the applied agent can be achieved by being absorved in the stratum corneum. Therefore, the best time for treatment is when the stratum corneum is at its weakest, e.g., during bathing, when the stratum corneum softens and its permeability increases. While some publicatons emphasizes the need of scrubbing before applying the treatment, there are others which indicate that this is unnecessary. This parasite seems to be very sensitive when removed from its natural environment. In our study, in which we took more than 300 samples, only 60 live parasites could be isolated and only 40 could be included in the *in vitro* experiments. We observed that they died instantly even when a minor trauma was caused with the needle tip. This was the reason why mites were removed with the help of a needle rather than with the skin scrapping method, as we were unable to remove live parasites with the curettage method. The parasite often settles on the wrists and ankles. Since the stratum corneum in this region is thicker than other regions, it is difficult for the active substance to reach under the skin (10). Making a pouch may thin the stratum corneum in this area and facilitate the spreading of the drug under the skin.

In the present study, it was shown that TTO has an acaricidal effect on *S. scabiei*. Although it was observed that the acaricidal effect increases with increasing concentration, it should be considered that it may cause irritation and treatment should be applied to the lowest concentration possible.

The comparative effect of these two agents was also evaluated in patients with rosacea, and both agents were found to be effective (12). In addition, the effectiveness of TTO and permethrin were evaluated in *in vitro* studies and it was found to be effective in the treatment of scabies (13). We wanted to emphasize that the combined use of these two agents, which we demonstrated *in vitro* in our study, will strengthen the treatment. Our *in vitro* study needs to be supported by *in vivo* studies. Side effects to TTO are known in human studies.

Walton et al. (13) who conducted a similar study with TTO stated that this chemical agent has an acaricidal effect, but they did not specify how long it takes to kill the parasite, while in the present study the time of death was observed in real time.

CONCLUSION

Our *in vitro* study also shows that TTO is effective against *Sarcoptes scabiei* parasite. Due to the toxic properties of scabicidal agents such as permethrin and ivermectin, the use of these agents in infants and children requires attention. Having formulations such as shampoo and shower gel might provide the opportunity to use TTO during the bath, where the stratum corneum is more permeable.

*Ethics

Ethics Committee Approval: The study was conducted in accordance with Helsinki Declaration principles. Ethical approval was obtained from İstanbul Medipol University (03/02/2022/73).

Informed Consent: Since the study was carried out on the waste sample, no approval could be obtained.

Peer-review: Internally peer-reviewed.

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