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NEW INNOVATION USING TOPICAL ITRACONAZOLS AS A SUPERFICIAL FUNGAL SKIN INFECTION THERAPY AND ITS SUPERIORITY COMPARED TO STANDARD THERAPY

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ABSTRACT

Background: Fungal infection of the skin is a common clinical problem in the community, particularly in groups of people who practice poor hygiene or in populations with a low immune status. Microsporon audoinii and Trichophyton rubrum, can cause the disease to be chronic and residif. This is generally due to the fungus developing a mechanism of resistance to the commonly used drug regimens in the community. As a result, a novel innovation is required to expedite patients' healing from dermatophytosis. Method: The purpose of this study is to compare the efficacy of a new treatment therapy utilizing a combination of 2% itraconazole, 1% salicylic acid, and 2% sulfur to that of 2% ketoconazole (standard therapy). The samples for this study were all cases of fungal infections of the skin diagnosed at Indra's clinic between 2016 and 2017. The study's independent variable was the formulation of the drug, while the dependent variable was clinical improvement and the occurrence of side effects. Results: The cure rate was 91,7 percent for the 121 respondents who received a combination cream containing 2% itraconazole, and 80.7 percent for the 114 respondents who received a ccream containing 2% ketoconazole. There were no statistically significant differences in adverse events between the two intervention groups. Finally, Innovative drug formulations for fungal infections (2 percent itraconazole, 1% salicylic acid, and 2% sulfur) have been shown to be more effective and superior to standard therapy.

Keywords: fungal infection; mycosis; dermatophytosis; itraconazole; ketoconazole

1. INTRODUCTION

Mycosis is a fungal infection. Fungi-caused diseases are classified into three types based on their mode of attack: deep mycosis, intermediate mycosis, and superficial mycosis. Under the skin, deep mycosis manifests clinical symptoms in the intestinal tract, respiratory tract, urogenital tract, cardiovascular system, central nervous system, muscles, bones, and occasionally the skin. This type of mycosis is uncommon because it is typically diagnosed as a chronic and residual disease in the clinic. Clinical manifestations of morphology may include tumor, vegetative inflammatory infiltration, fistula, ulcer, or sinus, either alone or in combination.[1–3]

Intermediate mycosis is a fungal disease that affects the skin layer (stratum corneum, hair and nails), and internal organs such as the vagina, skin, nails, bronchi, or lungs caused by the fungus Candida sp. Meanwhile, superficial mycosis is an infection caused by a fungus that attacks the

superficial area, namely the skin, hair, nails. The incidence of superficial mycosis is quite high in Indonesia because it attacks the wider community. This is because Indonesia is a tropical country with a hot and humid climate, the hygiene of some people is still lacking, there is a source of infection around it, the use of antibiotics, steroids and cytostatic drugs is increasing, there are chronic diseases and other systemic diseases.[4–8]

Superficial mycosis is classified into two types based on its etiology: dermatophytosis and non-dermatophytosis. Dermatophytosis is a fungal infection of the skin that is caused by the dermatophyte fungus. Because this group of fungi is attracted to keratin (keratinophilic), it can attack the skin's layers from the stratum corneurm to the basal stratum.[9,10]

This disease is a skin health problem for people around the world, especially in tropical countries and developing countries such as Indonesia. Human movement can rapidly affect the endemic spread of this fungus. Dermatophytosis affects all races, age groups, sexes and often recurs. The incidence of dermatophytosis in various medical teaching hospitals in Indonesia shows varying numbers. RSUD dr. Soetomo Surabaya reported 53.9% cases of dermatophytosis in 2010. In the same year Dr. Kariadi Semarang stated that dermatophytosis is 73.4% of all dermatomycoses. Dr. Hospital Wahidin Sudirohusodo Makasar reported that there were 69.33% new cases of dermatophytosis for the period 2006-2010. The data shows that dermatophytosis is a skin disease that ranks first compared to other skin diseases in RSUP H. Adam Malik and RSUD dr. Pirngadi Medan in 2002.[11,12]

Temperature, humidity, trauma, social conditions, lack of personal hygiene, tight clothing that does not absorb sweat, malnutrition, long-term antibiotic use, long-term corticosteroid use, and chronic disease are all factors that predispose a person to infection by fungi.[13–17]

Numerous standard therapies for dermatophytosis have been established. One of them is the topical application of a relatively simple drug, namely 2% ketoconazole cream or 2% miconazole cream. Therapy Certain fungi, such as Microsporon audoinii and Trichophyton rubrum, can cause a chronic and recurrent disease course even after they have been treated optimally. There are several interpretations of this incident, one of which is the possibility of drug resistance for superficial fungal infections as a result of frequent use of 2% ketoconazole and 2% miconazole creams. There was no data on drug resistance in the azole class against dermatophytosis fungal infections prior to the publication of this journal. Extrapolation of data on the number of azole groups resistant to candida fungi was performed.[18–20]

Epidemiological data indicate that infections caused by resistant fungal species, particularly Candida species resistant to fluconazole, are increasing. Additionally, the fungus that was previously considered a contaminant demonstrates resistance to all available antifungal agents and has the potential to cause invasive and life-threatening infections known as emerging fungi. Due to the prevalence of yeast infection and the scarcity of available

therapeutic options, antifungal resistance may become a serious problem in the future.[21]

Preventing fungal resistance and determining the best treatment for the patient are critical components of disease therapy. A novel innovation is required to expedite the healing process of patients with dermatophytosis. One such advancement is the topical application of itraconazole. The current treatment is oral itraconazole, which is extremely effective. Unfortunately, numerous cases of drug interactions, allergic reactions, and adverse effects have been reported with oral itraconazole. One possible solution is to switch from oral to topical itraconazole administration, which is typically safer, easier, and less expensive.

This journal summarizes the comparative effectiveness of topical itraconazole versus topical ketoconazole in the treatment of dermatophytosis.

2. METHOD AND MATERIAL

This was a retrospective cohort study in which we compared two different treatment formulations. This study included all cases of fungal infections of the skin seen at Indra's clinic between 2016 and 2017. The research sample is composed of individuals who meet the study's inclusion criteria. The study's inclusion criteria were a minimum age of 12 years and a dermatologist-diagnosed fungal infection of the skin. Incomplete medical record data or a history of azole drug allergy were used as exclusion criteria in this study. A minimum of 97 samples is required for each treatment formulation group (type 1 error is 5 percent and type 2 error is 20 percent). Non-random purposive sampling was used to collect data. The purpose of this study is to examine all patient medical record data from 2016 to 2017 for information on the diagnosis and treatment of fungal infections of the skin. The independent variable in this study was a topical formulation of ketoconazole 2% cream or a fungal formulation plus of itracolonazole 2%. In this study, the dependent variables were treatment success (improved or not), adverse events during treatment, and post-treatment symptoms. The two types of data analysis are descriptive data analysis and analytic data analysis. The proportion (percent) for the type of qualitative data and the distribution of centralized data (mean, SD, median, minimum, maximum) are included in descriptive data analysis. Analytical data analysis employed a comparative test for unpaired categorical data in the form of the Peason Chi Square test, the Chi Square with Yates Correction test, or the Fisher Exact test, as appropriate for each statistical test.

3. RESULTS

This study included 235 respondents with fungal infections of the skin. There were 121 respondents who received itraconazole 2% cream combination therapy and 114 respondents received ketoconazole 2% cream therapy. Patient demographic characteristics are presented in full in Table 1 for each group.

Table 1. Demographic Characteristics of Respondents

Variable	Treatment		p-value
	Itrakonazole 2% N : 121 respondent	**Ketokonazole 2% N : 114 respondent**	
Age	33,85 (12,72)	32,76 (13,66)	> 0,05
Sex • Male • Female	 54 (44,6%) 67 (55,4%)	 60 (52,6%) 54 (47,4%)	> 0,05
Hygiene • Good • Bad	 20 (16,53%) 101 (83,47%)	 21 (18,42%) 93 (81,58%)	
Commorbid disease • Diabetes Mellitus • Hypertension • Cardiovaskuler Disease • Kidney Disease • Hypercholesterol • Hyperuricemia • HIV/ AIDS • Autoimun	 13 (10,7%) 18 (14,8%) - - 26 (21,5%) 10 (8,3%) - -	 12 (10,5%) 16 (14%) - - 26 (22,8%) 9 (7,9%) - -	> 0,05

The therapy was given for 1 week and was re-examined at the next visit. Of the 121 respondents who received a combination cream containing 2% itraconazole, the cure rate was 91.7%, while 114 respondents who received a combination cream containing 2% ketoconazole obtained a cure rate of 80.7%. According to the Chi Square with Yates Correction statistical test, it was found that there was a difference in the level of clinical improvement from fungal infections to 2% of itraconazole when compared to 2% of ketoconazole. (p-value : 0,023)

Table 2. Therapeutic Effectiveness between 2 Treatment Regimens

Parametric	Clinical Improvement after 1 week		p-value
	Improvement	**Not**	
Itraconazole 2%	111 (91,7%)	10 (8,3%)	0,023
Ketokonazole 2%	92 (80,7 %)	22 (19,3%)	

Adverse effects were assessed for the use of 2 drug formulations for fungal infections of the skin. It was found that the only side effect symptoms were persistent itching and redness during the use of itraconazole 2% and ketoconazole 2%. The Fisher Exact

statistical test revealed that there was no significant difference in side effects between the 2 intervention groups. On the other hand, it was found that the use of itraconazole cream had the effect of reducing the incidence of post-inflammatory hyperpigmentation.

Table 3. Side effects between the 2 Treatment Regimens

Variable	Treatment		p-value
	Itrakonazole 2% N : 121 respondent	**Ketokonazole 2% N : 114 respondent**	
Adverse Effect			
• Persistent itching	9 (7,4%)	11 (9,6%)	> 0,05
• Redness	6 (5,0%)	10 (8,8%)	> 0,05
• Skuama	-	-	> 0,05
• Hyperpigmentation	22 (18,2%)	53 (46,5%)	< 0,05

4. DISCUSSION

Dermatophyte, candida, and malasezzia fungi cause superficial fungal diseases of the skin. Red, itchy, and scaly plaques are the primary symptoms of this fungal infection. Azole antifungals are effective against superficial fungal infections of the skin. This azole group is typically administered orally and in combination with topical preparations. The current azole classes that are most frequently administered orally are ketoconazole and itraconazole, while the most frequently administered topical preparations are ketoconazole and miconazole creams. Meanwhile, Itraconazole is still only used orally, and no topical preparation has been approved.[19,20,22–24]

While there have been numerous reports of resistance occurring during the oral and topical administration of the ketoconazole class, as well as during the administration of miconazole cream, there is something that concerns us more, and that is the reported side effects of ketoconazole on the liver, specifically hepatotoxicity.), and the WHO (Food and Drug Administration) have also prohibited the administration of Ketoconazole. The European Medicines Agency has recommended that ketoconazole be banned due to its potential to cause severe liver cell damage. Therefore, we require a new formulation that is more effective, efficient, affordable, and simple to use, while avoiding the side effects associated with the treatment of cases in people with fungal diseases, and which can be cured without the use of oral medications and only through topical administration, as the ketoconasole class cannot be given (is contraindicated) to children. Ketoconazole is contraindicated if the patient has a history of hypersensitivity to any of the drug's components. Due to the high risk of hepatotoxicity, ketoconazole is also contraindicated in patients at risk of liver problems. Additionally, ketoconazole is contraindicated when used in conjunction with quinidine, pimozide, cisapride, or methadone due to an increased risk of prolonging the QT interval.[25–29]

Epidemiological studies reveal that fungal infections frequently occur in children, pregnant women, diabetic patients,

patients undergoing treatment for other diseases, and patients undergoing drug therapy. which is quite a bit, so that if there is an active fungal topical therapy, oral givers can be avoided, which also results in a high number of drug interactions. Pharmacological studies indicate that when ketoconazole is combined with rifampicin, isoniazid, efavirenz, nevirapine, or phenytoin, it can cause a number of drug interaction effects, including the following: (1) Decreased blood levels of ketoconazole; (2) Increased effects of midazolam and alprazolam, which can make breathing difficult; (3) Increased levels of digoxin, fentanyl, and phenyto (5) Increases the risk of QT prolongation when used in combination with cisapride, quinidine, ranolazine, and terbenadine; (6) Increases the risk of muscle disorders when used in combination with lovastatin and simvastatin; (7) Increases the risk of bleeding when used in combination with dabigatran.[25,29–31]

On the other hand, Ketoconazole can cause side effects such as: (1) Nausea and vomiting; (2) Headache; (3) The eyes are sensitive to light; (4) Mood swings ; (5) Depression; (6) diarrhea; (7) Weight loss; (8) Changes in the menstrual cycle; (9) Decreased libido; (10) Breast enlargement in men. (11) Bruises and nosebleeds[25,29]

Currently, many ketoconazole therapy is replacing it with oral Itraconazole. The use of oral itraconazole also often causes various drug interactions and side effects for its users. This is a dilemma because itraconazole is a very effective drug for fungal infections. Drug interactions that often arise from the use of oral itraconazole are (1) Increased risk of arrhythmias when taken with cisapride, felodipine, halofantrine, mizolastine, pimozide, or tertenadine; (2) Increases the risk of ergotamine toxicity (ergotismus) when used with drugs containing ergot alkaloids, such as ergotamine; (3) Increases the risk of developing myopathy when used with cholesterol drugs with statins, such as simvastatin or atorvastatin; (4) Increase the sedative effect of triazolam or midazolam; (5) Lowering itraconazole levels when used with carbamazepine, phenobarbital, phenytoin, isoniazid, nevapirene, or rifampicin; (6) Decreasing the absorption of itraconazole in the blood when taken with antacids, PPI class drugs, or histamine H2 receptor antagonist drugs, such as ranitidine; (7) Increases the negative inotropic effect, namely the heart muscle relaxing effect of the drug verapamil; (8) Increases blood levels of itraconazole when combined with ritonavir, erythromycin, ciprofloxacin, or clarithromycin; (9) Increases the risk of developing serious respiratory problems when taken with fentanyl. While the side effects that often arise from using itraconazole orally are toxicity to the liver and decreased sex drive.[32]

Therefore, the formulation using itraconazole needs to be changed in order to achieve the best efficacy and reduce the possibility of adverse effects. One way is to change the route of administration from oral to topical. The advantages of using topical drugs are for local effects: minimal systemic side effects, preventing first-pass effects, and systemic effects such as IV infusion (zero order).[33,34]

The use of topical drugs that have been widely circulated is the use of ketoconazole or miconazole cream, which belongs to the first generation azole class. Various studies have shown that there are many resistance mechanisms to the first generation of azoles. Therefore, it is necessary to innovate new anti-fungal topical formulations in order to anticipate cases of resistance with as few side effects as possible. To maximize the efficacy, one of which is to innovate a new formulation with several types of supporting ingredients to achieve the above goals, namely the formulation of a new formulation with a combination of 2-3% itraconazole cream, 1-3% salicylic acid and 1-3% sulfur.

Itraconazole is a triazole antifungal that works by inhibiting ergosterol synthesis through inhibition of lanosterol 14α-demethylase. Itraconazole is a broad-spectrum antifungal and is effective for treating aspegylosis. Itraconazole is also known to have a role in cancer management through inhibition of the hedgehog pathway, but further research is needed.[35–40]

Sulfur (S16) is an element that is widely found and used in various types of industry. In dermatological preparations, the octasulfur (S8) form is generally used. Topical application of sulfur acts as a keratolytic, fungicid, bactericid. Sulfur is used in acne, seborrheic dermatitis, rosacea, scabies and various skin infections.[41–43]

Salicylic Acid (2- Hydroxybenzoic Acid / Orthohydrobenzoic Acid) is a member of the hydroxy acid group. Salicylic Acid can be extracted naturally or synthesized chemically. Topical salicylic acid functions as a keratolytic, comedilytic, reduces sebum production, antihyperplastic, desmolytic, antimicrobial and anesthetic. Salicylic acid as a keratolytic has been widely researched and used. At concentrations of 5% and above, this preparation has a rapid and deep keratolytic effect that causes desquamation. The underlying mechanism is that salicylic acid reduces the intercellular cohesion between corneocytes by dissolving the intercellular material and decreasing the pH of the stratum corneum, resulting in increased hydration and softening. The main goals of keratolytic use are hydration of the stratum corneum, desquamation of the skin, reducing itching, increasing penetration of topical drugs and phototherapy.[44–47]

The manufacture of night creams is carried out in accordance with the manufacturing standards for dermatological medicines. Formulations consisting of 2-3% itraconazole, 1-3% salicylic acid and 1-3% sulfur are crushed until smooth. The cream base consists of 30% lipowax, 60% distilled water, 3% aloe vera and 7% honey. The cream base is mixed gradually while stirring in a previously crushed formulation then placed in a container for cream. In the container, the method of use is stated.

This combined cream formulation has a synergic effect that is ideal for fungi pathogenesis, as it combines Itraconazole, which has antifungal properties, with sulfur, which also has fungicidal properties; sulfur also has keratolytic properties; salicylic acid, which is extremely useful to remove keratins from the skin, which are a staple food source for fungi, if the keratin is released through its sulfurous properties and salicylic acid, the fungus is deprived of its primary food source and thus cannot grow. As we know, salicylic acid, in addition to being keratolytic, also increases absorption through the skin, which means that administration of salicylic acid can accelerate the healing of fungal diseases. With the synergistic combination described above, it is hoped that it is extremely effective, efficient, inexpensive, and simple to apply, and can avoid hepatotoxic oral administration and drug interactions.

5. CONCLUSION

Topical itraconazole therapy has been shown to provide a higher rate of clinical improvement compared to topical ketoconazole therapy. The cure rate in the itraconazole cream therapy group was 91.7%, while the group receiving ketoconazole 2% had a lower cure rate of 80.7%. There were significant differences between the 2 therapy groups, and no significant differences in side effects were found between the 2 groups.

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