COMPARATIVE STUDY OF RECOVERY RATE OF TOPICAL CLOTRIMAZOLE AND POVIDONE-IODINE FOR CONTROLLING SUPERFICIAL FUNGAL SKIN INFECTION

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ABSTRACT

BACKGROUND

Topical agents are used to treat wound infections. Superficial skin fungal infections can be associated with many complications including involvement of the deeper layers and systemic manifestations in rare cases. Management of superficial skin infections can be challenging, and requires a close follow-up. Treatment options for this include local debridement, local and systemic antifungal agents and utilisation of topical antiseptics.

Aims and Objectives- The present work was aimed to find out the in vitro efficacy of different topical agents for wound pathogens. This study was designed to compare the recovery rate of superficial skin infections using two therapeutic methods; topical Betadine (Povidone-iodine) and clotrimazole.

MATERIALS AND METHODS

In this single-blind clinical trial, 300 patients with mycosis were selected using a non-probability convenient sampling method and were randomly assigned to two treatment groups of topical Povidone-iodine and clotrimazole (150 patients in each group). Response to treatment was assessed at 4, 10 and 20 days after treatment. Data were analysed using the independent t-test, Chi-Square and Fisher exact test in SPSS V18 software, at a significance level of $p < 0.05$.

Study Design- Randomly selected Gram-positive and Gram-negative bacterial isolates from infected wound cases admitted & outdoor were included in the in vitro activity testing.

RESULTS

The results showed that out of 300 patients with superficial skin mycosis, fungi type isolated included Aspergillus in 222 cases (74%), and Candida albicans in 159 patients (26%). On the fourth day after treatment, 39 patients (13.1%) in the group treated with Betadine and 27 patients (9.8%) in the group treated with clotrimazole showed a good clinical response to treatment ($p = 0.75$). A good response to treatment was reported for 130 (87%) and 69 patients (46.1%) on the tenth day after the treatment ($p = 0.02$); and 138 (92%) and 100 patients (67%) on the twentieth day after treatment ($p = 0.01$) in the groups treated with clotrimazole and povidone-iodine, respectively. The response to treatment was found to be more significant for clotrimazole.

CONCLUSION

In the present study, the efficacy of Povidone-iodine and clotrimazole was assessed for its efficacy and safety. The result of this study supports the use of clotrimazole, more effective antifungal in superficial skin fungal infection treatment, helping to avoid the emergence of resistant organisms.

KEYWORDS

Povidone-iodine, Clotrimazole, Recovery Rate.

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BACKGROUND

Superficial skin infections are becoming common. The most important reason for superficial skin infection is injudicious use of antibacterial agents.[1] Broad spectrum antibiotic like Tetracycline & Chloramphenicol use is one of the cause of superficial mycosis. It also occurs due to various local factors or as a manifestation of a systemic disease superadded by fungi. About 70% of people suffer from infection of the upper & lower extremity, 90% of which is unilateral.[2,3]

Superficial mycosis is associated with many complications including systemic manifestation of the inner ear with mortality due to septicaemia with superadded infection.[4] The mycosis can have a poor prognosis in immunocompromised individuals, especially in cases of cellular immunodeficiency and neutropenia. The disease presents many challenges, both for patients and for treating specialists, and may recur despite long-term treatment and follow-up.[5]

The main treatment of mycosis is the removal of visible debris and fungal elements. Topical medications recommended for the control of this condition include judicious use of steroids, antiseptics, acidic solutions, antifungal agents and driers. Antifungal medications of

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mycosis do not always cure the disease and in addition treatment should improve the physiological signs of external ear canal. Using boric acid in an alcohol solution for the treatment of disease is associated with 23% recurrence rate. Furthermore, using antifungal solutions, such as clotrimazole or nystatin, may be effective for the treatment of Candida infections, but Aspergillus infections respond poorly to treatment. This is while a wide range of fungi have been reported to cause mycosis and the most common species is Aspergillus. Therefore, an appropriate treatment regimen is necessary. On the other hand, widespread and unnecessary use of antibacterial treatment for mycosis may cause fungal overgrowth in this area, so the adverse effects of using wide-spectrum antibiotics are the secondary overgrowth of fungus and increasing prevalence of mycosis.

Given the importance of mycosis treatment as one of the challenge, this study aimed to compare the recovery rate of mycosis using topical Betadine and clotrimazole.

Agents which are used on living surfaces like skin and mouth are called as antiseptics. Infections in wound continue to be the primary source of morbidity and mortality. Growing multiple drug resistance among pathogens in wound infections is a major concern today. Wound colonisation with these organisms results in difficult of management of the wound, complicated by a greatly limited choice of therapeutic antibiotics. Nearly 40 million patients with superficial skin mycosis are treated annually in India.[1,2]

A Good Topical Antiseptic Should be-

1. Chemically stable.
2. Cheap.
3. Non-staining.
4. Agreeable odour.
5. Agreeable colour.
6. Bactericidal not merely bacteriostatic.
7. Additional activity against fungi, virus, protozoa.
8. Immediate onset of action.
9. Should act in presence of blood, pus, exudates.

The management of the microbial contamination of wound to prevent sepsis is a routine requirement of acute care that has led to the development of a variety of therapeutic agents for topical use. Prior to the advent of topical antimicrobial agents, the overall mortality rate in the typical burn population was reported as 38–45%. However, after the use of topical antimicrobial therapy, the overall mortality was reduced to 14–24%.[6] Further, the risk of development of superinfection and antibiotic-resistant bacteria, as well as organ toxicity, is minimal as compared to the use of systemic antibiotics in clean operations. The combination of systemic and topical chemotherapeutic drugs is a valuable adjunct in the treatment of contaminated wounds and high-risk patients.[7] The use of silver in wound management can be traced back to the 18th century, during which silver nitrate ($AgNO_3$) was used in the treatment of ulcers. Silver began to be used again for the management of burn patients in the 1960s, this time in the form of 0.5% $AgNO_3$ solution. Silver has the advantage of having broad antimicrobial activities against Gram-negative and Gram-positive bacteria and there is also minimal development of bacterial resistance. The use of these compounds and the mechanisms of silver resistance have been reviewed. One major advantage of its use is the limited side effect of topical silver therapy. [8]

Mechanism of Action of Antiseptics are[9]

1. Oxidation of bacterial protoplasm.
2. Denaturation of bacterial proteins including enzymes.
3. Increasing permeability of bacterial membranes.

Silver sulfadiazine (SSD) has been used clinically as a standard treatment for burns over the past three decades, since Fox first synthesised SSD from silver nitrate and sodium sulfadiazine for an increased potency and negligible adverse effects including minimal pain on application. At the present time, SSD is the most frequently used topical prophylactic agent on burn wound.

Many effective antibacterial substances are now available for topical application in the prophylaxis of sepsis in wound care. Other topical agents including mafenide acetate (Sulfamylon), bismuth tribromophenate (Xeroform),[6] Dakin's solution (0.25% sodium hypochlorite), bacitracin zinc, neomycin with polymyxin B and bacitracin (Neosporin), mupirocin (Bactroban), gentamicin sulphate, and nystatin have been used individually and in combination to control microbial growth in wounds and on healing meshed skin graft.[7] Other agents, such as nitrofuran or chlorhexidine preparations, may be useful in isolated clinical situations. Multiple topical agents may be used for cleansing, barrier protection, and antimicrobial control. However, occasional complications of contact and/or irritant dermatitis may further complicate re-epithelialisation and eventual wound healing. [8]

The goal of prophylactic topical antimicrobial therapy is to control microbial colonisation and prevent wound infection. In selected clinical circumstances, topical agents may be used to treat incipient or early burn wound infections.[9]

At present, the available preparations meet the majority of characteristics of an ideal topical agent. However, much effort must be put into finding better and more cost-effective products, especially for developing countries that experience burn accidents more frequently than developed nations. Hence, it was aimed presently to study the in vitro activity of various topical agents against the bacterial isolates from wound in India.[10]

MATERIALS AND METHODS

Study Group

This single-blind clinical trial was conducted on 300 patients with a definitive diagnosis of mycosis. After receiving permission from the Ethics Committee, the participants were selected. Patients with clinical signs and symptoms including pain, itching, mass, lesion on upper or lower extremity, stuffy feeling associated with inability to move the limb and discharge were considered suspicious for mycosis. The objectives of the study were explained to the participants and they were recruited into the study if they were willing to participate and had none of the exclusion criteria, including: longstanding uncontrolled diabetes, history of local surgery, history of treatment with antifungal agents and corticosteroids.

After recording the demographic characteristics such as age, sex, and obtaining informed consent, a total of 300 patients with mycosis were enrolled into the study and

recruited into one of the two treatment groups (150 patients in each group) by blocking randomisation. All 300 enrolled patients signed informed consent forms.

Collection of Samples

Samples were taken by a special speculum from the lesion on upper or lower extremity. Furthermore, in the presence of pus and mucus, these were also separated in a sterile container and sent to specialised laboratories of mycology.

Mycological Investigation

In the laboratory, the samples were evaluated by a microbiology specialist using KOH method, and the presence of fungal elements was considered as definite diagnosis of mycosis.

A portion of the sample was spread on a clean slide glass for direct examination and another sample inoculated in the Sabouraud dextrose agar (Merck, Germany) supplemented with chloramphenicol medium for fungal growth.[11] The plates were incubated at room temperature for two weeks. Fungi were identified by standard procedures. Furthermore, germ tubes on human sera and production of vesicles on corn meal agar (Merck, Germany) supplemented with Tween 80 (Sigma-Aldrich, Germany) were done for the identification of yeast. [12]

Recovery Rate of Mycosis

In the study, one patient group was treated with povidone-iodine so that at each visit, the patient's lesion was washed by the physician using 10 mL Betadine solution 10% with a syringe. The other group received 8 drops of antifungal clotrimazole, every eight hours. Patients were examined on 4, 10 and 20 days after treatment by a specialist who did not know about the type of treatment. The patients were categorised into three groups based on clinical response: good response (dry lesion, healthy granulation tissue and lack of secretion), partial response (slight discharge but not dry), and no answer (hypersecretion, wet lesion, painful). If complete response, the treatment was discontinued; otherwise treatment was continued. Finally non-responders were considered treatment-resistant on the twentieth day and treatment regimen was continued with Tolnaftate and Violet gentian.

Statistical Analysis

In the present study, to analyse the descriptive data, tables and charts of distribution frequency and for the inferential part, the independent t-test, Chi-square and Fisher exact test were used in SPSS V18 software. The significant level was considered at $p < 0.05$.

RESULTS

In this study, a total of 300 patients with mycosis were investigated in two treatment groups of Betadine and clotrimazole (150 patients in each group). Overall, 126 (42.15%) of the patients with mycosis were male and 174 (57.85%) were female. The average age of patients in two groups treated with Betadine and clotrimazole was 38.61 ± 15.45 and 40.37 ± 16.15 years old, respectively. In this study, Aspergillus spp. was responsible for 75.4% and Candida albicans for 24.5% of mycosis in the patient group treated with Betadine. Prevalence of Aspergillus spp. and C. albicans was reported for 72.5 and 27.5 percentages of patients with mycosis treated with clotrimazole.

Overall, the study showed no significant difference according to age ($p = 0.43$), sex ($p = 0.4$) and the causative agent of mycosis ($p = 0.63$) between two treatment groups of Betadine and clotrimazole.

Demographic Characteristics	Topical Povidone-iodine Group (%)	Topical Clotrimazole Group (%)	p-value
Age (years) Mean ± SD	38.61 ± 15.45	40.37 ± 16.15	0.43
Gender			0.40
Male	40 (39.2)	69 (45.1)	-
Female	90 (60.8)	81 (54.9)	-
Fungal agent			0.63
Aspergillus spp.	115 (75.4)	108 (72.5)	

Table 1. Comparison of Demographic Characteristics and Distribution of Fungi in Patients with Mycosis based on the Treatment Type

In the study, recovery rate of mycosis was evaluated in two treatment groups of Betadine and clotrimazole. The results demonstrated that on the fourth day after treatment, 13 patients (19.8%) in the group treated with Betadine and 13 patients (9.1%) in the group treated with clotrimazole had a good response to treatment ($p = 0.75$).

A good response to treatment was reported for 130 (87%) and 69 patients (46.1%) on the tenth day after the treatment ($p = 0.02$); and 130 (87%) and 69 patients (46.1%) on the twentieth day after treatment ($p = 0.01$) in the group treated with clotrimazole and povidone-iodine, respectively. It is noteworthy that in none of the patients treated with clotrimazole any side effects were observed. In our study, there was statistically significant difference in terms of response to treatment in the fourth, tenth and twentieth day after treatment between two treatment groups of Betadine and clotrimazole ($p < 0.05$) (Table 2).

Course of Treatment	Type of Treatment	Response to Treatment			p-value
		No Response (%)	Partial Response (%)	Good Response (%)	
4 days	Clotrimazole	47 (31.3)	82 (55.6)	13 (9.1)	0.75
	Povidone Iodine	46 (31.4)	88 (58.8)	13 (9.8)	
10 days	Clotrimazole	9 (6)	10 (7)	130 (87)	0.02
	Povidone Iodine	13 (8.8)	67 (45.1)	69 (46.1)	
20 days	Clotrimazole	2 (1)	10 (7)	138 (92)	0.01
	Povidone Iodine	13 (8)	37 (25)	100 (67)	

Table 2. Comparison of Response to Treatment on the Fourth, Tenth and Twentieth day after Treatment in Patients based on the Treatment Type

DISCUSSION

Superficial mycosis is one of the common diseases that are associated with many complications including involvement of the deeper tissues and mortality in rare cases due to superadded bacterial infection. The disease presents many challenges, both for patients and for doctor, and may recur despite the concern for long-term treatment and follow-up.

Results of this study showed that among 300 patients with mycosis, Aspergillus spp. was responsible for 74% (222 cases) and C. albicans for 26% (78 patients) of the infection. In the Pradhan et al study, Aspergillus species and C. albicans were reported as the most common species of fungi isolated from patients with mycosis in 2003.[13] The study conducted by Satish and colleagues showed that Aspergillus species (77%) was the most commonly isolated fungus in the immunocompetent group while Candida (53.4%) was commonly isolated in the immunocompromised group. In another study on 95 patients suspected of having the fungal infection, 72 cases of fungal cultures were positive and Aspergillus was identified as the most common fungus grown in culture (41.1%) and C. albicans was in the next grade, with a prevalence of 8.2%. The results of our study were consistent with the results above. Aspergillus species are one of the most common causes of opportunistic invasive fungal infections, especially otomycosis.[14] This may be due to its high prevalence in dust and the acidic nature of the ear canal, as Aspergillus species grow in pH 5 to 7.[15]

After completion of the treatment course in the present study, the results showed that on the fourth day after treatment, 55.6% and 58.8% of patients treated with Betadine and clotrimazole had partial response to treatment, respectively. In addition, on the tenth day after treatment, 49% of patients treated with povidone-iodine had partial response to treatment, and 46.1% of patients had a good response to treatment with clotrimazole. Finally, on the twentieth day after treatment, 68.6% of patients treated with Betadine and 66.7% of patients treated with clotrimazole had good response to treatment. Overall, in our study there was no statistically significant difference in terms of response to treatment in the fourth, tenth and twentieth day after treatment between two treatment groups of Betadine and clotrimazole. Regarding the antifungal treatment effect on mycosis, several studies have been conducted so far. In a single-blind randomised clinical study, the effect of Betadine 7.5% in comparison with clotrimazole 1% and lignocaine was evaluated on patients with otomycosis.[16] After the treatment period, in the Betadine patients group, the symptoms of itching, discharge from the ear, ear fullness, tinnitus and deafness were treated in 83.3%, 97.1%, 83.3%, 91.7%, and 91.7% of cases, and ear pain was treated in 100% of cases. While, in patients treated with clotrimazole and lignocaine drops, the symptoms of itching, ear discharge and fullness were cured in 93.3%, ear pain in 86.7% and tinnitus in 100% of cases. In another study, the therapeutic effect of miconazole ointment and clotrimazole drop was compared in patients with mycosis. All patients were examined for response to treatment one and two weeks after treatment. The results of the final analysis showed that and there was no difference in terms of response to treatment between the two treatment groups. Stern and colleagues demonstrated that clotrimazole was effective against most yeasts and molds but tolnaftate had no impact on otomycosis. In another study, clotrimazole and econazole were cited as the drug of choice in the treatment of otomycosis.[17]

According to the above-mentioned issues, it can be declared that the treatment of otomycosis is today one of the challenges facing ENT specialists, as a great number of fungal infections of external ear are resistant to the available antifungal drugs. Otomycosis treatment requires early detection and timely treatment of patients regarding the possibility of drug resistance in chronic infections. It should be noted that the basis of the treatment of otomycosis is keeping the ear dry and the ear hygiene, and the appropriate treatment protocol should be considered according to the different types of fungi causing the disease and sensitivity to different antifungal drugs. In our study, clotrimazole and povidone-iodine were used as two drug regimens for treatment of otomycosis. Clotrimazole is a medicine containing azole groups that is used to treat infections.[18] Betadine is also a remedy for infections that is easily accessible and its effect has been proven on chronic suppurative otitis media as the precipitating factors of otomycosis. This drug is a stable, inexpensive substance, and bacterial and fungal resistance to it has not yet been reported. Therefore, Betadine can be a good choice for otomycosis treatment in developing countries, due to its low cost, effectiveness and lack of ototoxicity.[19]

Although there is some controversy as to the effectiveness of topical chemotherapy in certain types of local infections, there are several clinical situations in which topical therapy is apparently beneficial. Topical antimicrobial formulations are widely used in the field of Dermatology.[20]

The primary purpose of the present study was to compare the various topical antimicrobial agents and the preparations, most of which are employed in the hospitals.[21]

Limitations of the Study

A randomised controlled comparative study with a much larger population may help to further substantiate the findings or reveal variations which were not observed in the present study.[22]

The cost benefit analysis was not done. The cost burden on the patient is also not analysed in this study as this can be influenced by various factors other than the cost of dressings. The quantitative assessment of the post-operative parameters like wound contraction, pain and residual raw ulcer area was also not included in the present study, which might have given a much better analysis of the efficacy of topical agents.[23]

Clinical progress of an ulcer varies according to the location of the ulcer; however, we have not tabulated the location of the ulcers in the present study. From wound culture mixed bacterial flora was grown which was not included in this study.[24] Skin graft take depends on lot of other inherent qualities of the ulcer, technical factors in skin grafting and the nutritional status of the patient which are not included in the present study. For a real controlled study, it would be best to treat two ulcers in the same patient using one as a control which was not considered in our study since this is not a controlled trial.[25]

CONCLUSION

From our study, we conclude that topical antiseptic by decreasing fungal load, forming healthy granulation tissue helps in better healing. Because of enhanced healing, overall hospital stay and post-operative complications were decreased. According to the results, efficacy of Povidone-iodine and clotrimazole regimens was analysed in treatment of mycosis. Our findings reinforce the use of clotrimazole for mycosis treatment due to high effectiveness and appropriate therapeutic effect on Aspergillus species and C. albicans, the most common causes of superficial mycosis. Such treatment can help to avoid the emergence of resistant organisms.

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