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Study to determine the efficacy of Clotrimazole 1% cream for the treatment of onychomycosis in association with the mechanical reduction of the nail plate

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Abstract

Onychomycosis is invasion of the nail by dermatophytes yeasts and moulds [Calderon RA, Hay RJ. Fungicidal activity of human neutrophils and monocytes on dermatophyte fungi *Tri. Quinckeanum* and *Tri. Rubrum*. *Immunology* 1986;61:289–95; Degreef H. Onychomycosis. *Br J Clin Pract Syn Suppl* 1990;71:91–7; Zaias N. Clinical manifestations of onychomycosis. *Clin Exp Dermatol* 1992;17(1):6–7]. Causative organisms include *T. rubrum* and *T. mentagrophytes*. Fungi invade the distal and lateral under surfaces of the nail. The prevalence of onychomycosis approximates to 5–10% of the population and is increasing significantly in recent years [Stutz A. Allylamine derivatives—a new class of active substances in antifungal chemotherapy. *Angew Chem* 1987;2:320–8].

Clotrimazole 1% cream is the most commonly prescribed topical antifungal agent in the United Kingdom although its use on nails has not been widely documented. Past inefficiencies may be due to the thickness of the nail plate. The mechanical reduction of the nail minimises the nail as a barrier to the absorption of the cream and increases the permeability of the nail plate.

Subjects were ambulant and healthy with no systemic medication, no past history of anti-fungal agents and an ankle-brachial index indicating sufficient circulation for healing to occur. The infecting organism was identified by microscopy and culture. A total of ninety-two infected nails were isolated over a four-year period. The age range was 60–78 years. Nails were drilled every 14 days by the same operator and the area of infection mapped. Clotrimazole 1% cream was applied twice daily during the trial period and the percentage clearance rate was recorded. After 12 weeks there was an average improvement of 96.2% with the infection in 80% nails completely resolved.

Keywords: Onychomycosis; Clotrimazole 1%; Drilling

1. Introduction

Onychomycosis is invasion of the nail plate by dermatophytes, non-dermatophyte filamentous fungi, yeasts and moulds [1–3]. Tinea unguium is a more specific term referring only to those infections caused by dermatophytes [1,5]. These dermatophytes include fungal infections, for example, tinea pedis and yeast infections such as candida albicans. Causative organisms for tinea pedis include, *T. rubrum* 85% [1], *T. mentagrophytes* 12% and *E. floccosum* 2–3% [6] of cases. The prevalence of *T. rubrum* is higher in females (71.2%) than in males (53.8%) [6]. However, the percentage age of females was significantly higher than males and it is known that the incidence of onychomycosis increases with age. Onychomycosis usually succeeds a tinea pedis infection of the webbing [1,3,7], which presents as peeling, masceration and fissuring interdigitally [1].

The main portal of entry for dermatophyte infections is through the distal and lateral undersurfaces of the nail bed [7,8]. Invasion succeeding tinea pedis of the webbing is primarily via plantar skin through the hyponychial epidermis then secondarily into the nail bed epidermis. The eponychium, or cuticle, consists of a narrow band of epidermis extending from the margin of the nail fold onto the nail plate. This is watertight preventing invasion by microorganisms. However, damage by trauma or manicuring may provide portals of infection [6,9].

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Onychomycosis with symptoms accounts for 40% of all nail diseases [2]. The prevalence of onychomycosis is unknown as many cases are undiagnosed. It is estimated that 5–10% of the population are infected [2,6,10], although estimates may be as high as 10–15% [1]. The incidence of observed mycoses has increased significantly in recent years. This may be due to an increase in the number of infections, to improved methods of diagnosis or to a better awareness of hygiene [4]. Roughly 99% of fungal infections are produced by dermatophyte infections. These are all capable of producing onychomycosis [11].

Diagnosis is made by collecting nail clippings and scrapings [1]. Collection of samples should be from the affected portion of nail obtaining as much crumbling material as possible. Infection is most concentrated on the under surface of the nail at the point where it adjoins normal nail at the advancing edge. Where nail dystrophy has occurred it is necessary to obtain samples by scraping techniques. A scalpel is used to obtain affected portions from the nail bed. As much nail material as possible should be obtained and folded in black paper. The samples should be sent to microbiology as soon as possible for microscopy and culture [1,7].

Clotrimazole is the most commonly prescribed topical antifungal in the United Kingdom for the treatment of tinea pedis [12]. It is active against dermatophytes, dimorphic fungi and yeasts and possesses prominent antibacterial activity [13]. It has a recommended dose or two to three times daily. The aims and objectives of this study were to establish the efficacy of Clotrimazole 1% cream for the treatment of onychomycosis in association with the mechanical reduction of the nail plate. The best possible outcome was to mycologically cure the nail as shown by negative microscopy and culture.

2. Methodology

Ethical approval was sought and was initially rejected as the original proposal included a control group who just had their nail drilled. It was rejected as it was thought unethical to exclude patients with a specific pathology from treatment. The revised proposal, without control group, was accepted for ethical approval from the committee. Subjects included in the study had to satisfy the exclusion and inclusion criteria. Those included were ambulant males and females between the ages of 60 and 78 years. Those with systemic disease, or those taking medications, which may have contra-indicated the use of Clotrimazole cream, were excluded from the study. The subjects were not to have had any previous treatment with antifungal agents.

Subjects undertook a pre-experimental vascular assessment. To satisfy the inclusion criteria all the pulses had to be present, capillary refill time had to be shown to be normal, the lower limb to be warm with a healthy colour. There was to be no evidence of oedema, ischaemia or claudication. An ankle-brachial index was performed and a value of ≥ 1 was required. This determined adequate blood supply to the appendages to allow normal healing to occur. Diagnosis of onychomycosis was based on clinical evidence of infection and potassium hydroxide microscopy and Dermasol culture from the infected nail. This confirmed the presence of the infecting organism and allowed identification of the dermatophyte. Any evidence of inter-digital tinea pedis excluded subjects from the trial as this would have been a further source of infection.

Written consent was obtained from all subjects. For the purpose of this study there were 26 subjects with a total of 92 infected nails. The number of infected nails was recorded and the area of infection measured. This was performed by sticking clear tape on to the nail, drawing around the area of infection and estimating the total area by sticking the tape over 1 mm^2 graph paper. The areas were measured three times by different operators and an average area calculated.

The entire surface of the nail was thinned using a burr to plane down the nail plate thickness, thus minimising the nail barrier for the absorption of the cream. This was performed by the same operator to maintain a uniform thickness on all subjects. Subjects returned every 14 days for further thinning of the nails and for measurement of the infected area. The subjects were instructed to apply Clotrimazole 1% cream to the infected nails twice a day. An instruction sheet was provided outlining any possible side effects and the subjects were regularly questioned on possible local side effects or any observations on the treatment.

Subjects were instructed to continue applying the cream even after the infection had appeared to have resolved. Fungal spores posses immense resistance to environmental stresses such as heat, desiccation and radiation. This serves to prolong the life of the cell in environmental conditions, which are no longer conductive to growth.

The outcome of the treatment was assessed by the percentage increase or decrease in the total area of infection. At the point of complete disappearance of the infections nail clippings were sent for microscopy to establish the presence or absence of fungal elements.

3. Results

Forty subjects were selected for the purpose of this study, 28 males and 12 females. Two subjects complained of pain and erythema following the application of the cream after one week and were excluded from the study. Twelve subjects were found to be non-compliant with follow up appointments and were also excluded. This left 26 subjects (65%), 16 males and 10 females, aged 60–78. There were a total of 92 infected nails.

The most commonly affected nails were the left hallux (19.6%) and the right hallux (16.3%). Of the infected toes 21% were the second toe, 16% the third toe, 12% the fourth and 10% the fifth. 61.5% of the subject sample (16 subjects) were diagnosed with positive culture and microscopy to have