

Effectiveness of 3 per cent boric acid in 70 per cent alcohol versus 1 per cent clotrimazole solution in otomycosis patients: a randomised, controlled trial

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Abstract

Objectives: To compare the clinical effectiveness and adverse events for 3 per cent boric acid in 70 per cent alcohol versus 1 per cent clotrimazole solution in the treatment of otomycosis.

Methods: A total of 120 otomycosis patients were randomly assigned to receive either 1 per cent clotrimazole solution (intervention group) or 3 per cent boric acid in 70 per cent alcohol (control group) at the Khon Kaen Hospital ENT out-patient department. Treatment effectiveness was determined based on the otomicroscopic absence of fungus one week after therapy, following a single application of treatment.

Results: After 1 week of treatment, there were data for 109 participants, 54 in the clotrimazole group and 55 in the boric acid group. The absolute difference in cure rates between 1 per cent clotrimazole solution and 3 per cent boric acid in 70 per cent alcohol was 17.9 per cent (95 per cent confidence interval, 2.3 to 33.5; $p = 0.028$) and the number needed to treat was 6 (95 per cent confidence interval, 3.0 to 43.4). Adverse events for the two agents were comparable.

Conclusion: One per cent clotrimazole solution is more effective than 3 per cent boric acid in 70 per cent alcohol for otomycosis treatment.

Key words: Boric Acids; Clotrimazole; Otomycosis; Otitis Externa; Mycoses; Antifungal Agents

Introduction

Otomycosis is a superficial fungal infection of the external ear canal. It is a worldwide disease, but is more common in tropical zones.¹ Predisposing factors are: a warm and humid environment, swimming, an immunocompromised host (e.g. diabetic mellitus, acquired immune deficiency syndrome, leukaemia, and bone marrow transplant and dialysis patients), pregnancy, post-canal wall down mastoidectomy, tympanic membrane perforation, hearing aid wearing, self-inflicted injuries (e.g. by cotton swabs), and previous use of topical antibacterial or steroid preparation.^{2,3} Otomycosis has been reported to affect 15–20 per cent of otitis externa cases.⁴

In Khon Kaen Hospital, in Thailand, otomycosis has been reported in 11 per cent of patients presenting with otitis externa symptoms or inflammatory conditions of the ear canal. Standard treatment consists of ear canal cleaning with fungus removal, combined with the application of topical antifungal drugs to the ear canal. There are two groups of topical antifungal medications, a specific group, such as clotrimazole, miconazole and

nystatin, and a non-specific group, such as acetic acid, boric acid and gentian violet.⁵

Currently, there is still no consensus as to the most effective drug for otomycosis.^{2,4,6} Three per cent boric acid in isopropyl alcohol is a commonly used antiseptic for acute otitis externa treatment. It has been found to be effective, with a mycological cure rate of around 72.5 per cent.⁴ One per cent clotrimazole is a specific antifungal drug that has proved effective for otomycosis in around 94.12 per cent of cases.⁵

As there has been no comparative study of 1 per cent clotrimazole solution and 3 per cent boric acid in 70 per cent alcohol as medications for otomycosis, this study aimed to compare the effectiveness and adverse events associated with these two otomycosis treatments.

Materials and methods

Materials

Commercial 1 per cent clotrimazole solution (Candid[®]) was used as the treatment intervention and 3 per cent boric acid in 70 per cent alcohol (prepared by the

pharmaceutical department of Khon Kaen Hospital) was used as a control. Both drugs were clear solutions and were put into identical bottles.

Study participants

Inclusion criteria were: symptomatic patients with otomycosis, aged more than seven years, with microscopic findings of fungus and a potassium hydroxide smear of ear discharge that was positive for fungus.

Exclusion criteria were: pregnancy; tympanic membrane perforation; previous mastoid surgery; co-infection (e.g. severe otitis externa, rhinosinusitis or tonsillitis) which needed other antimicrobial medications; previous use of topical antibiotic or steroid medication; systemic antifungal drug use within the two weeks prior to the study; allergy to 1 per cent clotrimazole solution or 3 per cent boric acid in 70 per cent alcohol; and those had the tendency to loss follow up after one week of the treatment.

All eligible patients received information about the study, including the potential benefits and risks, and only those who gave written informed consent were enrolled.

Randomisation

Random permuted blocks of sizes 4 and 6 were employed, using Microsoft Office Excel[®] 2007 software. The generated sequences were inserted into sealed envelopes. The enrolled patients were randomly assigned to the two groups (clotrimazole group or boric acid group) with an allocation ratio of 1:1.

In cases of bilateral otomycosis, the flipped unbiased coin method was used to randomly assign one ear to the study, but both ears received the same treatment. Neither doctors nor patients knew which topical medication was being employed.

Procedure

Before the medications were applied, all patients underwent ear cleaning to remove all fungal debris. This was achieved using suction under the operating microscope. The medication was then instilled into the ear canal by a well-trained nurse according to the allocation sequence and left for 5 minutes. Treatment involved a single application of medication.

Participants were asked to report any adverse effects of the treatment. They were informed to keep their ears dry, to avoid further trauma to their ears, and to avoid using any other systemic or topical antifungal or antibiotic medications. During the follow-up period, if any other illness occurred, they were asked to inform the investigator so that other interventions could be considered. Any such interventions were recorded in case they had an effect on the treatment outcome. The investigator and participants were blinded to the treatment intervention.

Participants attended a follow-up appointment at one week post-treatment for evaluation of the treatment outcome. This was carried out by the same investigator,

who examined the ear canal under the operating microscope. Regarding treatment outcomes, patients were classified as cured (absence of fungus) or not cured (presence of fungus).

This study was approved by Khon Kaen Ethics Committee (registry number KKH24-01-2555) and was registered through ClinicalTrials.gov (NCT01547221).

Statistical analysis

To detect a 20 per cent difference in cure rates between 1 per cent clotrimazole solution and 3 per cent boric acid in 70 per cent alcohol, with a two-sided significance level of 5 per cent and with 80 per cent power, a total sample size of 92 participants (46 in each group) was estimated to be required. This was based on assumptions that boric acid efficacy is 75 per cent (in line with the overall mean efficacy reported in various studies)^{4,7,8} and that clotrimazole efficacy is 95 per cent (in line with the overall mean efficacy reported in previous studies).^{9–15} Assuming that 10 per cent of participants would be lost to follow up, 57 participants in each group were required to achieve 80 per cent power. In fact, a total of 120 participants were enrolled in the study.

Outcome analysis was performed using the intention-to-treat principle. Treatment effectiveness and adverse events in both treatment groups were analysed and reported as rates, with absolute differences and 95 per cent confidence intervals (CIs), and *p*-values. The number needed to treat was also reported.

Results

Patients

From January 2012 to April 2015, of 553 otomycosis patients screened, 120 were eligible for participation. These participants were randomly assigned to receive either 1 per cent clotrimazole solution (57 patients) or 3 per cent boric acid in 70 per cent alcohol (63 patients). Eleven participants (three in the clotrimazole group and eight in the boric acid group) were lost to follow up, for unknown reasons (Figure 1).

The baseline characteristics of the two treatment groups were balanced, with the exception of infection site (clotrimazole was more frequently used in the left ear and boric acid in the right ear), as shown in Table I. A female predominance was noted in both groups. Participants' median age was 41 years (interquartile range, 31–57 years) in the clotrimazole group and was 40 years (interquartile range, 29–54 years) in the boric acid group.

The median duration of symptoms prior to treatment was one week in both groups. The most common presenting symptoms were aural fullness (91.2 per cent and 90.5 per cent in the clotrimazole and boric acid groups respectively) and itching (83.6 per cent and 85.5 per cent), followed by otalgia (64.3 per cent and 62.9 per cent) and otorrhoea (44.6 per cent and 50.0 per cent), as shown in Table I.

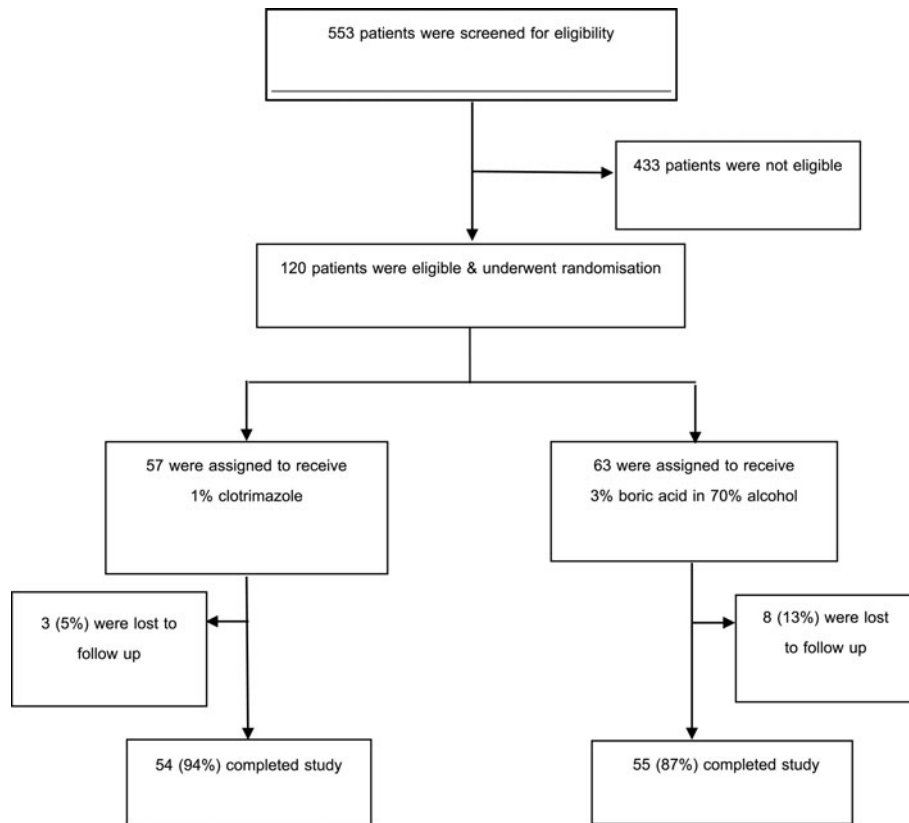


FIG. 1

Assessment for eligibility, randomisation and outcome.

The most common precipitating cause of otomycosis was self-induced trauma (83.9 per cent and 80.3 per cent in the clotrimazole and boric acid groups respectively), followed by water in the ear (46.3 per cent and 38.6 per cent) and a foreign body (insect) in the ear canal (12.3 per cent and 11.1 per cent).

TABLE I
BASELINE CHARACTERISTICS

Characteristic	1% Clotrimazole solution*	3% Boric acid in 70% alcohol†
Sex – female (n (%))	33 (57.9)	41 (65.1)
Median age (IQR); years	41 (31–57)	40 (29–54)
Infection site – right ear (n (%))	24 (42.1)	40 (63.5)
Median symptom duration (IQR); days	7 (4–8.5)	7 (4–14)
Symptoms (n (%))		
– Otalgia	36/56 (64.3)	39/62 (62.9)
– Itching	46/55 (83.6)	53/62 (85.5)
– Aural fullness	52/57 (91.2)	57/63 (90.5)
– Otorrhoea	25/56 (44.6)	30/60 (50.0)
Precipitating cause (n (%))		
– Self-induced trauma	47/56 (83.9)	49/61 (80.3)
– Water in ear	25/54 (46.3)	22/57 (38.6)
– Other (foreign body)	7/57 (12.3)	7/63 (11.1)

*Total n = 57; †total n = 63. IQR = interquartile range

Primary outcome

Three participants in the clotrimazole group and eight participants in the boric acid group were lost to follow up. This left 109 participants at the 1-week follow up, 54 participants in the clotrimazole group and 55 participants in the boric acid group. The cure rate was 85.2 per cent (46 participants) in the clotrimazole group and 67.3 per cent (37 participants) in the boric acid group. The absolute difference in cure rates between the two groups was 17.9 per cent (95 per cent CI, 2.3 to 33.5; $p = 0.028$), which was significant, as shown in Table II. The number needed to treat was 6 (95 per cent CI, 3.0 to 43.4).

Secondary outcome

Table III shows a summary of the adverse events after treatment. The absolute differences in the frequency of events between the two groups were: -9.2 per cent for a burning sensation (95 per cent CI, -2.0 to 1.6 ; $p = 0.054$), -11.1 per cent for irritation (95 per cent CI, -21.3 to -0.8 ; $p = 0.022$), 11.3 per cent for itching (95 per cent CI, -2.2 to 24.8 ; $p = 0.949$) and -1.1 per cent for other symptoms (such as otalgia and aural fullness) (95 per cent CI, -9.4 to 7.3 ; $p = 0.400$). The only statistically significant difference between the two groups was for irritation.

Discussion

The results of our randomised, double-blind, controlled study showed that 1 per cent clotrimazole solution is

TABLE II
PRIMARY OUTCOME: TREATMENT RESULTS*

Treatment outcome	1% Clotrimazole solution (n (%)) [†]	3% Boric acid in 70% alcohol (n (%)) [‡]	Absolute difference in cure rates (% (95% CI))	<i>p</i>
Cured	46 (85.2)	37 (67.3)	17.9 (2.3 to 33.5)	0.028
Not cured	8 (14.8)	18 (32.7)	-17.9 (-33.7 to -2.7)	0.028

*At one week post-treatment. [†]Total *n* = 54; [‡]total *n* = 55. CI = confidence interval

TABLE III
SECONDARY OUTCOME: ADVERSE EVENTS*

Adverse event	1% Clotrimazole solution (n (%)) [†]	3% Boric acid in 70% alcohol (n (%)) [‡]	Absolute difference in event frequency (% (95% CI))	<i>p</i>
Burning sensation	3/54 (5.6)	9/61 (14.8)	-9.2 (-2.0 to 1.6)	0.054
Irritation	2/54 (3.7)	9/61 (14.8)	-11.1 (-21.3 to -0.8)	0.022
Itching	13/57 (22.8)	7/61 (11.5)	11.3 (-2.2 to 24.8)	0.949
Other (otalgia, aural fullness)	3/57 (5.3)	4/63 (6.4)	-1.1 (-9.4 to 7.3)	0.400

*After treatment application. [†]Total *n* = 57; [‡]total *n* = 63. CI = confidence interval

significantly more effective than 3 per cent boric acid in 70 per cent alcohol in the treatment of otomycosis (absolute difference in cure rates of 17.9 per cent; 95 per cent CI, 2.3 to 33.5; *p* = 0.025). In our study, the effectiveness of 1 per cent clotrimazole solution in otomycosis treatment was 85.2 per cent. Other prospective or randomised, controlled trials have demonstrated success rates of 75–100 per cent.^{2,10,12–14} The effectiveness of boric acid for otomycosis varies between 63 and 80 per cent in the literature,^{4,7,8} while in our study it was 67.3 per cent. The variation in reported effectiveness may be due to differences in application methods and treatment durations. Mgbor and Gugnani demonstrated that 1 per cent clotrimazole, given every other day for 7–10 days, was effective in 75 per cent of cases.¹² Jadhav *et al.* administered the treatment three times a day for one month, and reported effectiveness of 100 per cent.¹⁴

Currently, there is still no consensus regarding the most effective agent,^{2,4,6} and the most appropriate duration of treatment with antifungals has not been established.⁴ The efficacy of azoles seems to depend on treatment duration,⁵ but our study has shown that a single application of the drug is also effective one week after treatment.

Effective otomycosis treatment requires not only the use of topical antifungal agents, but also the elimination of predisposing factors and ear cleaning with effective removal of fungal debris from the ear canal. Chalabi and Ahmed stated that meticulous cleansing, especially cleansing of the anterior meatal recess, is an important aspect of otomycosis treatment.¹⁶ Our study entailed meticulous cleaning with removal of fungus under the operating microscope. Furthermore, advice was given to patients to minimise predisposing factors.

Although 3 per cent boric acid in 70 per cent alcohol is cheaper than 1 per cent clotrimazole, the clotrimazole

was more effective and caused less ear irritation than the boric acid (3.7 per cent vs 14.8 per cent).

Regarding clinical presentation, aural fullness was the most common presenting symptom of otomycosis in our study, followed by ear itching, otalgia and otorrhoea. Other studies have reported that the three most common presenting symptoms are otalgia, aural fullness and ear itching respectively.^{5,16}

- **Otomycosis can be medically treated with many topical antifungal drugs**
- **Medications include 3 per cent boric acid in 70 per cent alcohol and 1 per cent clotrimazole ear drops**
- **This study showed that a single application of 1 per cent clotrimazole was more effective than 3 per cent boric acid in 70 per cent alcohol**
- **The absolute difference in cure rates was 17.9 per cent (95 per cent confidence interval, 2.3 to 33.5) at one week follow up**

The main limitation of our study was the lack of longer-term follow up to identify clinical relapse.

Conclusion

One per cent clotrimazole solution is more effective and less irritating than 3 per cent boric acid in 70 per cent alcohol when used as a topical medication for otomycosis in the form of a single application. This indicates that a single application of the medication can be an effective treatment option for otomycosis.

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