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Main Articles

Randomized controlled trial on the treatment of otitis externa with one per cent silver nitrate gel

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Abstract
Otitis externa (OE) and especially otomycosis can be very persistent and difficult to control. In the present study the efficacy of treatment of OE with a single instillation in the ear canal of one per cent silver nitrate in three per cent hypromellose gel compared to 0.1 per cent silver nitrate gel was tested in a single-blinded randomized controlled parallel group study. The outcome measure was complete resolution of the OE after one week. Forty-four patients with refractory, bacterial as well as fungal, OE entered the study, comprising 30 ears in each treatment arm. Eight patients defaulted from follow-up, five ears in each treatment arm. A single instillation of one per cent silver nitrate gel cured 23 (92 per cent) of 25 ears with OE, whereas with 0.1 per cent silver nitrate gel seven (28 per cent) of 25 ears treated were cured (Fisher-exact test, p-exact = 0.00010). In a non-controlled series of 120 ears 93.3 per cent needed only a single instillation of one per cent silver nitrate gel while another five per cent were cured after a second instillation a week later. There were no adverse reactions. OE can be treated effectively with instillation of one per cent silver nitrate gel and is particularly useful in recalcitrant otomycosis. The treatment method saves both cost and time.

Key words: Otitis Externa; Silver Nitrate; Therapy

Introduction

Uncomplicated diffuse otitis externa (OE) is commonly treated with ear toilet and administration of an antiseptic, antibiotic or antifungal preparation with, or without, a steroid.[1–3] Multiple visits to the practitioner are usually necessary before the condition clears up. Otomycosis, in particular, can be very persistent and intensive and prolonged treatment may be needed. Daily application with clotrimazole cream for a period of two weeks was needed to obtain 96 per cent cure in a study in Nigeria.[4] In a study in Turkey instillation of four per cent boric acid in alcohol twice daily for two weeks with frequent suction cleaning resulted in a cure rate of 77 per cent.[5] In a study in Spain daily suction cleaning and administration of ciclopiroxolamine cream, ciclopiroxolamine solution or boric acid for two weeks resulted in a clinical cure rate of 60 per cent, 65 per cent and 80 per cent respectively.[6] In acute OE medicated ribbon gauze was more cost-effective than ear wicks with fewer follow-up visits and a resolution rate of 70 *versus* 64 per cent.[7] These treatment modalities are time consuming. Boric acid and alcohol can be very painful on non-intact skin. Adherence to drug regimens is questionable in general. Eardrops are often not taken according to the prescribed regimen[8] and patients may default from follow-up visits for various reasons. For many patients travel distances up to 1000 km within Botswana to the Ear Clinic (workplace of the first author) are a major obstacle to keeping follow-up appointments. With these problems in mind, a treatment of OE was developed with a single or a repeated instillation of one per cent silver nitrate in three per cent hypromellose gel. Silver nitrate has been used for treatment of OE in the past, but only in a caustic concentration of 20 per cent.[9,10] Silver nitrate at a concentration of one per cent was chosen because this concentration is non-caustic and has been used for many years in prophylactic one per cent eye drops in neonates. Silver nitrate solution of 0.1–1 per cent has been used on infected burns. Examples of the use and microbiological activity of silver nitrate and other silver compounds have been reviewed elsewhere.[11–15] Silver ions bind avidly to tissue proteins, causing structural changes in bacter-

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TABLE I
RESULTS OF TREATMENT OF OE WITH 1% SILVER NITRATE GEL IN A NON-CONTROLLED SERIES

Cured after one instillation	93.3% (112 of 120 ears)
Cured after a second instillation	5.0% (6 of 120 ears: all otomycosis)
Not cured after the second instillation	1.7% (2 of 120 ears: both otomycosis)

ial cell walls and intracellular and nuclear membranes. These lead to cellular distortion and loss of viability. Silver binds to bacterial DNA and RNA and denaturates it, thereby inhibiting replication (reviewed in 13 and 15).

A gel was chosen in order to provide a sustained release of silver ions to the ear canal skin as the gel dries up and also to prevent the silver nitrate running out of the ear, which would cause temporary dark stains on the skin and permanent stains on textiles.

Hypromellose three per cent in Ringer's lactate has been used in eye surgery as a visco-elastic agent and is used in a concentration of 0.3 per cent as artificial tear drops. In the present formulation Ringer's lactate would have been unsuitable, as the chloride would have produced immediate precipitation of the photo-labile silver chloride. Instead, distilled water was used. In 2000 a consecutive non-controlled group of 97 referred patients with 120 ears with OE were followed-up at the Ear Clinic of the first author (unpublished observation). These patients had refractory OE that had not responded to initial treatment with acidifying antiseptic ear-drops elsewhere. Some patients are cured with these drops, but otomycosis in particular does not respond in many cases. The microbiological findings in this group were, in descending order, fungus (62 per cent: *Aspergillus fumigatus*, *niger* and *flavus*), Gram-negative bacteria (20 per cent: mainly *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus* sp.), yeast (12 per cent: *Candida* sp.) and Gram-positive bacteria (six per cent: mainly *Staphylococcus aureus*). Treatment consisted of instillation of one per cent silver nitrate gel after ear toilet. This instillation was repeated after one week if necessary. Most patients were cured after a single instillation (Table I).

The cure rate of 93.3 per cent with a single instillation and the absence of side effects such as pain, granulations and desquamation made us continue with this treatment method until present. However a controlled study of the efficacy of this treatment method was lacking.

The objective of the present study is to test the efficacy of the treatment of OE with a single instillation of one per cent silver nitrate gel in a single-blinded randomized controlled parallel group study. The control group received a low concentration of 0.1 per cent silver nitrate, which is still, at least *in vitro*, anti-microbiologically active. This was preferred over a placebo consisting of three per cent hypromellose gel without any silver nitrate.

Methods

The gel was prepared by adding three per cent hypromellose powder to a solution of one per cent or 0.1 per cent silver nitrate in distilled water while stirring until a smooth gel forms. The gel is kept in amber glass bottles and stored in the dark. The one per cent solution is light brown as a result of trace amounts of free silver due to photo-degradation, while the 0.1 per cent solution is almost colourless.

Patients

A consecutive series of 44 patients with 60 affected ears referred to the Ear Clinic of Bamalete Lutheran Hospital in Ramotswa, Botswana were enrolled into the trial in the first quarter of 2003. All patients had been referred for treatment of refractory chronic OE or acute exacerbation of a recurrent or chronic OE. Included were patients of all ages with diffuse acute or chronic OE, independent of pre-treatment. The human immunodeficiency virus (HIV) status of the patients was not a parameter in this study. Patients with peri-auricular cellulitis, eardrum perforations, polyps and radical mastoid cavities were excluded. Participation was on a voluntary basis. Each patient gave informed consent before entering the trial.

Randomization

A list of random A's and B's was computer-generated with Excel in such a way that the total of A's equalled the total of B's. The ears in group A received one per cent silver nitrate gel. The ears of group B received 0.1 per cent silver nitrate.

Blinding

The patients were blinded from the treatment arm to which they were allocated. The ENT-surgeon (first author), who did the assessment and the treatment, could not be blinded effectively due to the colour difference of the two gels and also because a difference in discolouration of the meatal skin could be observed at the follow-up assessment.

Intervention

A swab from the affected ear canal was taken for aerobic bacterial culture except in cases of obvious macroscopic fungus. Anaerobic culture was not done. The ear canal was meticulously cleaned by suction and mopping using the examination microscope. The allocation of the ears was carried out after the ear examination and ear cleaning by opening a sequenced envelope that contained the code A or B. In case of bilateral OE each ear might be allocated to the same or to a different treatment group. The ear canal was filled with one of the two gels. A 5 ml disposable syringe with Luer-lock connection to a 2 mm or 1.5 mm Ø House suction tip was used. Usually a little less than 1 ml of gel was sufficient to fill an adult ear canal. The porus of the ear canal was blocked with cotton wool. The patient

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TABLE II
MICROBIOLOGICAL DISTRIBUTION OF THE EARS WITH OE

	Fungus	Bacteria	Yeast	No growth	Total
Group A	9	11	3	2	25
Group B	8	14	3	0	25

was instructed to remove the cotton wool the following day when the gel had dried up. Acute cases with severe pain received an analgesic. Re-assessment was done after seven days. In those cases of group B (0.1 per cent silver nitrate gel) where after the first week no cure was obtained, treatment was changed to one per cent silver nitrate gel.

Outcome measure

The outcome measure was complete healing after one week of the OE with micro-otoscopically confirmed normalization of the skin and absence of debris, pus or fungus.

Results

Eight out of the 44 patients who entered the trial defaulted from re-assessment a week later, comprising five of 30 ears of group A and five of 30 ears of group B. Thirty-six patients with 25 ears in each treatment arm remained for analysis. These were 33 adults (age range 20–68, average 36.4) and three children below eight (five months, 1.5 and seven years). There were 14 females and 22 males. The microbiological distribution in each group is shown in Table II.

Monocultures were found in all except one ear that had *Staphylococcus aureus with E. coli*. There were 19 Gram negative strains: *Pseudomonas aeruginosa* (10×), *Pseudomonas pseudomallii* (1×), non-lactose fermenting coliform bacteria (3×), *E. coli* (1×), *Proteus* sp. (2) and *Bacillus* sp. (2×) and six Gram positive strains: *Staph. aureus* (3×), *Staph. epidermidis* (2×) and α-haemolytic streptococci (1×). Six ears had *Candida* sp. Two of the cultures had no growth. The 17 ears with otomycosis showed macroscopically *Aspergillus fumigata* (nine), *Aspergillus niger* (seven) and *Aspergillus flavus* (one). The majority of these ear canals were fully blocked with fungus. Eleven of the 50 ears had an acute oedematous, bacterial OE. The cure rates are shown in Table III.

Of group A all ears with bacterial OE (11 ears), with yeast (three ears) and without growth (two ears) were cured, while seven out of nine ears with fungal OE were cured. Of group B four of 14 ears with bacterial OE, three of eight ears with fungal OE and none of three ears with yeast were cured. The difference in cure rate between the two groups is statistically significant (Fisher-exact test, p-exact = 0.000010). Following the intention-to-treat principle and assuming the worst-case-scenario (all five dropouts of group A not cured and all five dropouts of group B cured) the difference in cure rate is still statistically significant (Fisher-exact test, p-exact = 0.006762).

Discussion

The cure rate in the study is in accordance with the cure rate in the previous non-controlled series. The high percentage of otomycosis in this study should not be seen as an indication of a generally high prevalence of otomycosis in the relative dry country of Botswana. One may expect that bacterial OE is more often successfully treated in the Primary Health Care sector than the more persistent otomycosis. Therefore patients with otomycosis are more likely to be referred. Meticulous ear cleaning is essential, as with all other forms of topical treatment especially in cases of otomycosis. Residual growth of fungus is mainly seen in the difficult-to-access anterioinferior recess near the eardrum. The gel is easy to make and cheap: the ingredients of a single 1 ml instillation cost a few eurocents. In most cases a single instillation is sufficient. The silver nitrate gel has also a good anti-oedematous action due to the hygroscopic property of hypromellose. Topical steroids are not necessary. Culture and sensitivity tests are not of practical significance in uncomplicated OE. Adverse effects such as pain, inflammatory reactions, reactive granulations, ulcerations and discharge were not encountered. A brown staining of the ear canal skin is usually seen due to formation of metallic silver under influence of light, without forming a slough of the outer (keratin) epidermal cells as happens with a caustic 20 per cent solution.[10] The stains disappear from the skin in a couple of weeks. Silver nitrate even in a concentration of 20 per cent does not penetrate the outer epidermis as biopsy specimens have revealed.[10] Silver toxicity is not expected with the small amount of silver nitrate instilled in the ear canal. Toxic effects of silver nitrate on the skin, such as argyria, electrolyte depletion and methaemoglobinaemia, have only been described after prolonged treatment of large areas of burned skin.[16–18] Silver nitrate is not significantly absorbed from the skin.[19] No signs of silver poisoning have appeared in patients almost

TABLE III
RESULTS OF TREATMENT OF OE WITH 1% SILVER NITRATE GEL WITH A SINGLE INSTILLATION OF 1% VERSUS 0.1% SILVER NITRATE GEL

	Group A (1% silver nitrate gel)	Group B (0.1% silver nitrate gel)
Cured	92% (23 of 25 ears)	28% (7 of 25 ears)
Not cured	8% (2 of 25 ears, both fungal)	72% (18 of 25 ears: fungal, bacterial and yeast)

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totally covered with 0.5 per cent silver nitrate dressings for 50–150 days.[20] At this point we must draw attention to the fact that silver nitrate is unsuitable for use in the middle ear as middle-ear secretions will immediately cause silver nitrate to precipitate in the form of insoluble silver chloride and silver complexes, which would abolish the antimicrobial effectiveness. It can be concluded that treatment of OE with silver nitrate gel is effective and saves both cost and time. The method is particularly useful in the treatment of recalcitrant otomycosis.

- **The control of otitis externa can often be difficult**
- **The author of this paper, in a controlled trial, reports the clinical efficacy of two differing strengths (0.1 and one per cent) of silver nitrate gel in a hypromellose base instilled into the ear canal. Data from a non-controlled study appears to have acted as the catalyst for this trial**
- **No adverse effects from this therapy were found and a high success rate is reported with solutions containing the higher concentration of silver nitrate. The therapy is, it is suggested, particularly useful in otomycosis**

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