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A meta-analysis comparing the efficacy and safety of different modes of administration of cream in the treatment of otomycosis

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Review Article

Da-Zhong Yan takes responsibility for the integrity of the content of the paper

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Abstract

Objective. To assess the efficacy and safety of two different modes of administration, external ear canal filling and smearing, in the treatment of otomycosis.
Methods. A computerised search of relevant published studies in the China National Knowledge Infrastructure, China Biology Medicine, Web of Science, PubMed, Embase and Cochrane Library databases that include randomised controlled trials or clinically controlled trials on the same drug in different modes of administration for the treatment of otomycosis.
Results. Seven studies with 934 patients were included. The filled group had a higher clinical efficacy (relative risk = 1.18, 95 per cent confidence interval (CI) 1.12–1.24, $p < 0.0001$) and a lower recurrence rate (relative risk = 0.29, 95 per cent CI 0.18–0.47, $p < 0.0001$) compared with the smear group, and there was no significant difference in the adverse effects (relative risk = 0.61, 95 per cent CI 0.34–1.12, $p = 0.11$).
Conclusion. Current evidence suggests that the efficacy of the delivery modality of the external auditory canal filling treatment is significantly better than external auditory canal smearing.

Introduction

Otomycosis is a common superficial fungal infection of the ear that accounts for approximately 10–20 per cent of ear canal infections. The majority of the pathogens are those with the potential to cause diseases, with the two most prevalent being Aspergillus species and *Candida albicans*.[1] Risk factors for otomycosis include humid climates, the presence of cerumen, exposure to polluted water, frequent ear plucking, immunocompromised hosts and the recent increase in the use of topical antibiotics and/or steroidal drugs. Its symptoms comprise ear itching, ear stuffiness, ear discharge, ear pain, hearing loss, tinnitus and other related symptoms.[2,3] Recurrent episodes are difficult to treat and interfere with patients' ability to go about their daily lives and jobs.

The most common way of treating the disease at the moment is to clean the external auditory canal while also applying antifungal medications locally. Cream formulations are preferred over liquid formulations because they are less likely to cause systemic irritation and provide a longer duration of local action following application. Moreover, they reduce the risk of drug penetration into the middle ear, making them a safer option for patients with perforated eardrums.[4]

There are two main modes of administration for cream formulations: external ear canal filling and smearing. Filling refers to the use of a syringe to inject the medication thoroughly into the external ear canal, ensuring that the medication comes into full contact with the infected area. Smearing, on the other hand, involves using tools such as cotton swabs to apply the medication on the skin surface of the external ear canal. However, as yet there has not been a thorough evaluation of how these two medication delivery methods compare. To provide a demanding theoretical foundation for clinical decision-making, we conducted a meta-analysis to clarify the efficacy and safety of these two therapy methods.

Materials and methods

The protocol for this study was prospectively documented on Prospero (ID CRD42023454286).

Search strategy

A computerised search for relevant published studies was carried out in the China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), Web of Science, PubMed, Embase and Cochrane Library databases using keywords such as otomycosis, otomycosis, fungi and randomised controlled trial (RCT). The deadline for

publication of all literature was August 2023, and there was no restriction on the language of the publication. The researchers excluded irrelevant articles by skimming titles and abstracts and by reading the full article.

The literature search process was conducted by two independent researchers. Using Embase as an example, the search formula was ('ear mycoses'/exp OR 'ear mycoses' OR 'ear mycosis'/exp OR 'ear mycosis' OR 'fungal ear infection'/exp OR 'fungal ear infection' OR fungal ear infections'/exp OR 'fungal ear infections' OR fungal infection of the ear'/exp OR 'fungal infection of the ear' OR 'fungal infections of the ear'/exp OR 'fungal infections of the ear' OR 'fungal otitis'/exp OR 'fungal otitis' OR 'mycotic ear infection'/exp OR 'mycotic ear infection' OR 'mycotic otitis'/exp OR 'mycoticotitis' OR 'otomycoses'/exp OR 'otomycoses' OR 'otomycosis'/exp OR 'otomycosis') AND ('randomized controlled trial'/de)

Eligibility criteria and study selection

The researchers searched for all research comparing the effects of external ear canal filling and smearing. The following standards were fulfilled by all the included studies: (1) the study was an RCT; (2) the study population had been clinically diagnosed with otomycosis[5]; (3) treatment was localised medication (the experimental group used the filling technique and the control group used the smearing technique, both groups used the same drug); and (4) the measured outcomes were the patients' clinical effectiveness rate, recurrence rate and adverse effects (including ear itching, ear swelling, ear pain, etc.) after drug administration.

The exclusion criteria were: (1) studies including other diseases of the external or middle ear with similar symptoms and imaging changes, such as osteoma of the external auditory canal, cholesteatoma of the external auditory canal and globoid tumours of the middle ear; (2) studies involving surgical treatment or animal research; (3) repeat studies; and (4) literature with incomplete data or no research indicators.

Data extraction

Data extraction was carried out by two independent researchers, Lei Fan and Xuemeng Xu, and any disagreements were resolved through discussions or with input from a third researcher. The extracted data encompassed general information, including the first author, publication date, country, gender and age, as well as clinical data, such as the sample size for each group and relevant outcomes, such as cure rate, recurrence rate and adverse effects. The literature screening was conducted using Zotero 6.0 software and valid data were extracted using an Excel spreadsheet, which was then cross-checked by another investigator.

Quality assessment

As the included literature all involved RCTs, we evaluated them using the risk of bias assessment tool provided in the Cochrane Systematic Evaluator's Handbook 5.1.0, and plotted the risk of bias using the R 4.3.1 software robvis package. We separately evaluated random sequence generation, allocation concealment, blinding of subjects and studies, blinding of study results, completeness of results, selective reporting of results, other sources of bias. Differences were discussing between the researchers and other authors for help if required.

Statistical analysis

Because the outcome indicators we chose were all dichotomous variables, the intervention effect was estimated by calculating the relative risk and 95 per cent confidence interval (CI). The raw data were statistically analysed using the meta package of R 4.3.1 software and the Q test was used to test for heterogeneity between studies. When the p value of the Q test[6] was more than 0.1 and the I^2 value was less than 50 per cent, the studies were homogeneous and the fixed-effects model was applied. However, if the p value of the Q test was less than or equal to 0.1 and the I^2 value was more than or equal to 50 per cent, this indicated that there was heterogeneity among the studies so the random-effects model was used. Possible heterogeneity was analysed according to predefined subgroups. Sensitivity analysis was performed to evaluate the stability and reliability of the meta-analysis results and to evaluate the publication bias of the included literature with the help of funnel plots.

Results and analysis

Literature screening

According to the initially formulated strategy, the number of articles retrieved from each database was PubMed 21, Embase 22, Web of Science 66, CBM 139, Cochrane Library 72, CNKI 174, China Clinical Trial Registry 0, US Clinical Trial Registry 10, a total of 504. After 160 articles that were duplicates, the total number of articles was 344. After reading the titles and abstracts, 25 articles were initially screened for full-text evaluation, and after implementing strict inclusion and exclusion criteria, seven RCTs were finally included, one in English and 6 in Chinese. The process and the results of the literature screening are shown in Figure 1.

Characteristics of inclusion studies

The 7 studies included were RCTs with a total of 934 patients. All seven of these studies included the outcome metric clinical effectiveness, four studies included recurrence rates and four studies included adverse events. In one of the articles the patients had a mean age of less than 18 years, and in the other studies the patients had a mean age of more than 18 years. The included articles described the age, gender and basic conditions of the patients, and the differences were not statistically significant. The characteristics of the included literature are shown in Table 1.

Quality assessment

The Cochrane Handbook of Systematic Evaluation was used to evaluate the quality of the seven included studies. The results of the risk of bias evaluation of the included RCTs are shown in Figures 2 and 3.

Outcomes

Clinical efficacy

The evaluation criteria were categorised as cured, apparent effect, effective and ineffective, and the total effective rate = (cured + apparent effect + effective)/total number of cases × 100 per cent. There were seven studies[7–13] of clinical efficacy, including 934 patients: 510 in the experimental group and 424 in the control group. The forest plot is shown in

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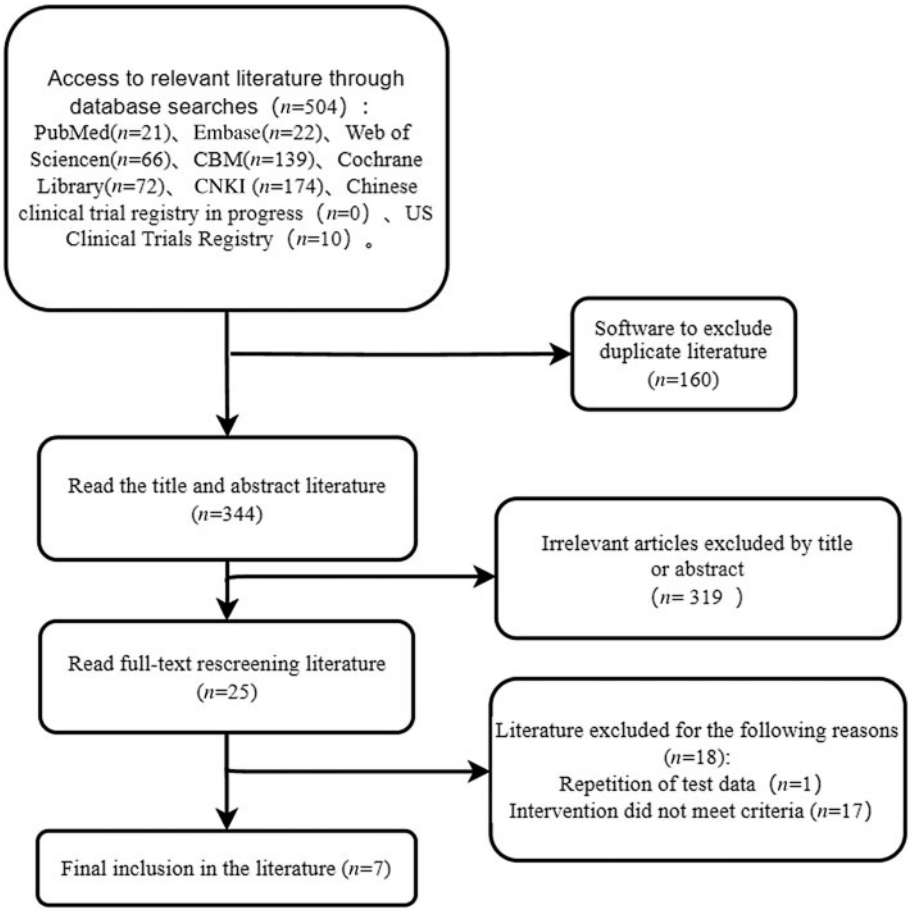

Figure 1. Study flow chart. CBM = China Biology Medicine; CNKI = China National Knowledge Infrastructure.

Figure 4. The results of the heterogeneity test were I^2 equal to 0 per cent and p equal to 0.74, indicating that there was no significant heterogeneity among the studies therefore the fixed-effects model was used for meta-analysis. The relative risk was 1.18 (95 per cent CI 1.12–1.24, $p < 0.0001$). Meta-analysis showed that there was a statistically significant difference in the clinical efficacy rate between the experimental group and the control group. The results showed that the clinical effective rate of the filled group was significantly higher than that of the smearing group.

Recurrence rate

In the comparison of recurrence rates, 4 studies[8,10–12] were included with 627 patients, 352 in the filled group and 274 in the smearing group. The forest plot is shown in Figure 5. The results of the heterogeneity test showed that I^2 was 0 per cent and p was 0.50, indicating that there was no significant heterogeneity among the studies therefore the fixed-effects model was used for meta-analysis. The relative risk was 0.29 (95 per cent CI 0.18–0.47, $p < 0.0001$). Meta-analysis showed that there was a statistically significant difference in the recurrence rate between the experimental and control groups. The results showed that the clinical recurrence rate in the filled group was significantly lower than that in the smearing group.

Adverse reaction

The comparison of adverse reactions included 4 studies[9,10,12,13] with 528 patients, 279 in the experimental group and 249 in the control group, and the forest plot is shown in (Fig. 6). The results of the heterogeneity test showed that I^2 was 74 per cent and p was less than 0.01, suggesting that the heterogeneity between the literature selected for this study was statistically significant and that a search for heterogeneity should be performed. Meta-analysis was performed using a random-effects model, and the relative risk was 0.61 (95 per cent CI 0.34–1.12, $p = 0.11$). Meta-analysis showed that there was no statistically significant difference between adverse reactions in the experimental group and the control group. There was no difference in the incidence of adverse reactions between the filled and smearing groups.

Subgroup analysis

Subgroup analysis of mean age

Clinical effectiveness, recurrence rate and adverse reactions were used as indicators, and the mean age was analysed in subgroups with a cutoff of 18 years. Adverse reactions were dropped from this subgroup analysis because the mean age in all studies was greater than 18 years. In the subgroup with mean age greater than 18 years, the clinical effectiveness rate was significantly higher in the filled group compared with the smearing group (relative risk = 1.18, 95 per cent CI 1.12–1.25) and the recurrence rate was significantly lower in the filled group compared with the smearing group (relative risk = 0.31, 95 per cent CI 0.19–0.51). In the subgroup with mean age less than 18 years, the filled group had a significantly higher clinical effectiveness rate compared with the smearing group (relative risk = 1.22, 95 per cent CI 1.04–1.43) and for the recurrence rate in the filled group compared with the smearing group (relative risk = 0.13, 95 per cent CI 0.02–1.04) the results were not statistically significant. These results are shown in Table 2.

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Table 1. Characteristics of the included literature

First author	Year	Study design	Sample size (T/C)	Male (*n*), female (*n*)	Average age ± SD (years)	Medicines	Interventions		Outcome*	Intervention duration
							T	C		
Donghui Huang	2014	RCT	30/27	35, 22	32.62 ± 5.8	Nystatin cream	Filling	Smearing	1	2 weeks
Guanquan Li	2017	RCT	30/30	36, 24	5.4 ± 1.45	Triamcinolone acetonide and econazole nitrate cream	Filling	Smearing	1, 2	10–14 days
Xiangbao Zhang	2017	RCT	43/38	38, 43	35.38 ± 1.20	Triamcinolone acetonide and econazole nitrate cream	Filling	Smearing	1, 3	2 weeks
Xiaoyu Wang	2019	RCT	51/51	63, 39	37.19 ± 11.31	Triamcinolone acetonide and econazole nitrate cream	Filling	Smearing	1, 2, 3	2 weeks
Yongqi Li	2019	RCT	152/104	133, 123	35.1	Triamcinolone acetonide and clotrimazole cream	Filling	Smearing	1, 2	2–3 weeks
Yuhui Zeng	2022	RCT	113/89	97, 105	36.63 ± 14.64	Triamcinolone acetonide and econazole nitrate cream	Filling	Smearing	1, 2, 3	1 week
Wenrong Lou	2022	RCT	48/48	55, 41	46.7 ± 9.8	Triamcinolone acetonide and econazole nitrate cream	Filling	Smearing	1, 3	2 weeks

*1, clinical efficacy; 2, recurrence rate; 3, adverse reaction. T = Test group; C = Control group; RCT = randomised controlled trial

Subgroup analysis of whether endoscopy was used

Clinical effectiveness, recurrence rate and adverse effects were used as indicators of clinical effectiveness and were categorised into two subgroups: endoscopically applied and self-applied. Recurrence rate was dropped from this subgroup analysis because all studies were self-applied. In the subgroup without endoscopy, the clinical effectiveness in the filled group was significantly higher than that of the smeared group (relative risk = 1.18, 95 per cent CI 1.11–1.24), and in terms of adverse effects, there was no statistically insignificant difference in the filled group compared with the smeared group (relative risk = 0.79, 95 per cent CI 0.60–1.06). Among the endoscopy subgroups, the filled group had a significantly higher clinical effectiveness rate than the smearing group (relative risk = 1.25, 95 per cent CI 1.05–1.49), and the filled group had significantly fewer adverse reactions than the smearing group (relative risk = 0.27, 95 per cent CI 0.15–0.51). This subgroup analysis resulted in a significant reduction in adverse reaction heterogeneity. These results are shown in Table 3.

Results of the sensitivity analysis

The sensitivity analyses of the findings were performed using the method of sequential exclusion of individual literatures. Adverse reactions were reversed and the remaining meta-analysis results were not reversed, suggesting that the combined results were essentially stable, as shown in Table 4. A forest plot of the adverse reactions that were reversed is shown in Figure 7.

Publication bias analysis

A funnel plot of clinical effectiveness rate, recurrence rate and adverse reactions showed that the symmetry of the distribution of the scatter across the studies in the plot was poor, as illustrated in Figure 8. The use of Egger's test was abandoned because of the inclusion of fewer than 10 studies.[14] These results suggest that there may be publication bias in the selected literature.

Discussion

The aim of this study was to compare the efficacy and safety of the two main modes of administration of cream in the treatment of otomycosis (filling and smearing). Our findings suggest that in the treatment of fungal infections of the external auditory canal, patients using filled therapy perform better in terms of clinical effectiveness and recurrence rates, and that the valuation of clinical effectiveness and recurrence rates is reliable in sensitivity analyses. However, there was no significant difference between filled and smearing treatments in terms of adverse effects, and sensitivity analyses were not stable. In the subgroup analyses we also found that age may be associated with the recurrence rate, and the different methods of application also seem to be associated with the occurrence of adverse reactions.

There are several explanations for why filled treatments perform better relative to smearing treatments in fungal infections of the external auditory canal: (1) Increased area of drug contact: filling treatment usually fills the external auditory canal fully with the drug, thus ensuring that the drug is in full contact with the infected area, which can increase the concentration of the drug in the infected area and reach the

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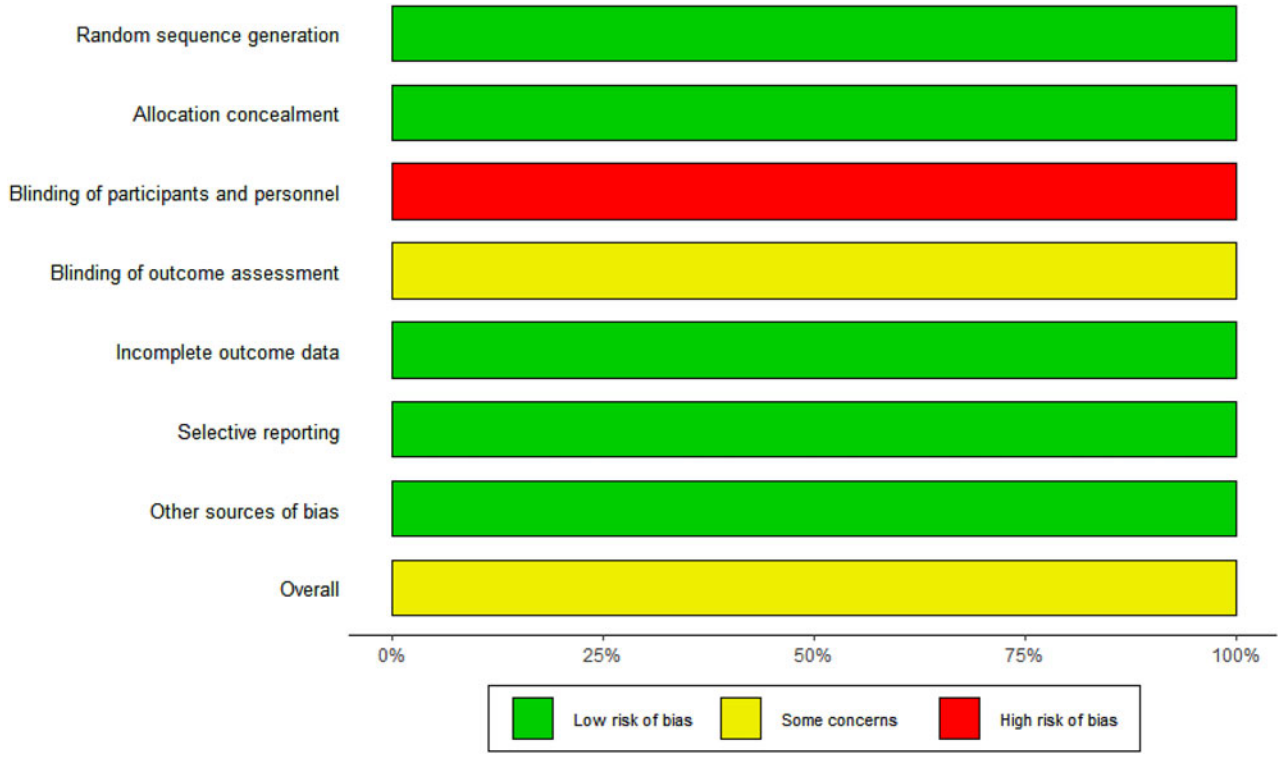

Figure 2. Risk of bias graph.

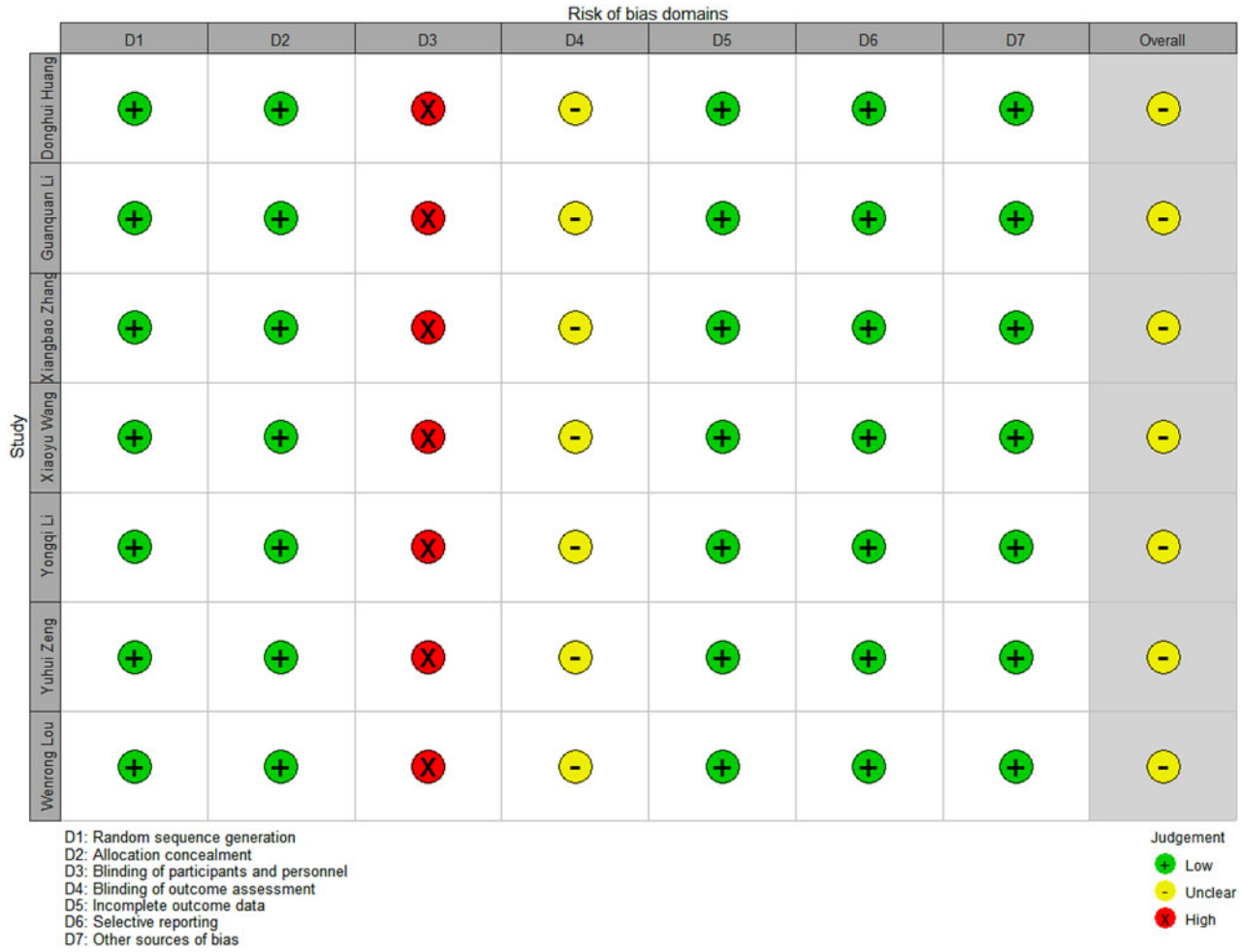

Figure 3. Risk of bias summary.

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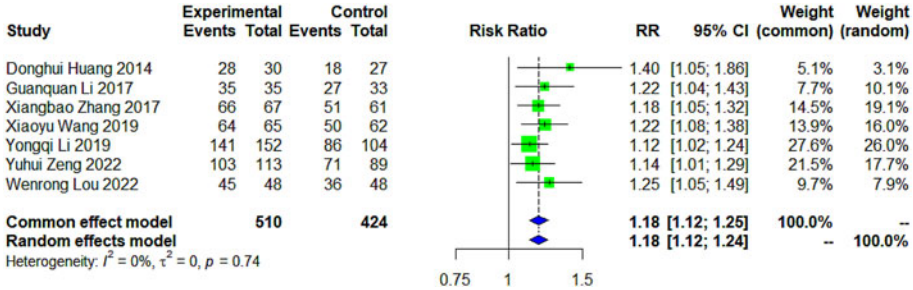

Figure 4. Comparison of clinical effectiveness rates. RR = relative risk; CI = confidence interval.

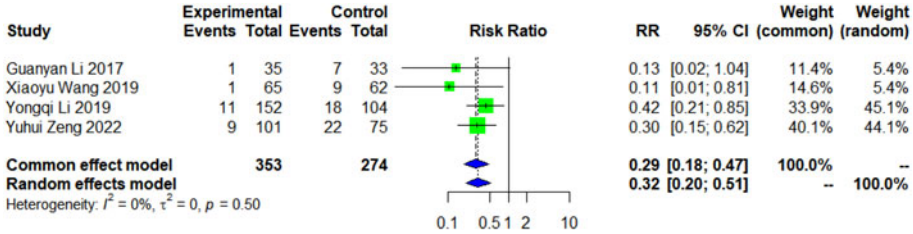

Figure 5. Comparison of recurrence rates. RR = relative risk; CI = confidence interval.

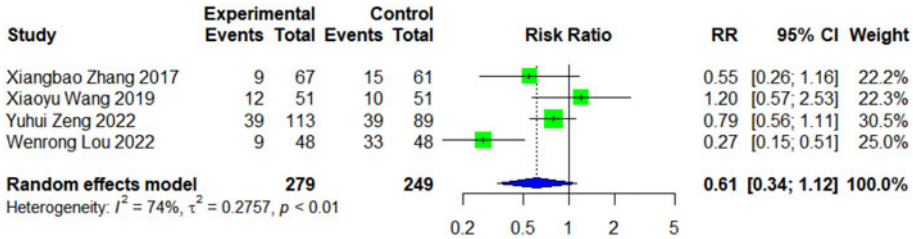

Figure 6. Comparison of adverse reactions. RR = relative risk; CI = confidence interval.

Table 2. Subgroup analysis of mean age

Outcome indicator	Subgroup age (years)	Number of studies included	Heterogeneity I^2 (%)	Heterogeneity p	Effect model	Outcome RR (95% CI)	Test for subgroup differences Q	Test for subgroup differences p
Clinical efficacy	>18	6	0	0.65	Fixed effect	1.18 (1.12–1.25)	0.14	0.71
	<18	1	–	–	Fixed effect	1.22 (1.04–1.43)		
Relapse rate	>18	3	0	0.43	Fixed effect	0.31 (0.19–0.51)	0.63	0.43
	<18	1	–	–	Fixed effect	0.13 (0.02–1.04)		

RR = relative risk; CI = confidence interval; Q = Q-Test

fungus-infected area more efficiently to kill or inhibit the growth of the fungus; (2) Sustained efficacy: filled treatment usually requires the medication to be retained in the external auditory canal for a period of time, therefore, compared with smear treatments, the medication has a longer contact time and is released at a relatively slower rate, which helps to maintain a stable concentration of the medication, effectively inhibiting fungal growth and reducing the risk of recurrence; (3) Patient compliance: because application of the ointment may cause pain or discomfort, especially if the external auditory canal is already damaged or the inflammation has worsened, the patient may be reluctant to adhere to the treatment because of the pain or be reluctant to use the treatment medication; (4) Lifestyle and time constraints: the patient's lifestyle and work schedule may not allow them to consistently apply the ointment on a daily basis, whereas filled treatments require a lower frequency of dosing; (5) Individual differences: differences in the shape and physiology of the external auditory canal from patient to patient may result in inconsistent application of the treatment, and some patients may not be able to apply the medication effectively or the medication may not be easily retained in their external auditory canal.

A subgroup analysis of adverse reactions by application method revealed that within-group heterogeneity was significantly lower than overall heterogeneity of adverse reactions in all subgroups, so the application method may be the main reason for high heterogeneity of adverse reactions. Some studies[9] showed that the most common adverse effect was ear pain, which may be due to the repetitive manipulation of the skin of the external auditory canal with otomicroscopic ear microtomes. In a subgroup analysis of age, it was revealed that the recurrence rate was lower in adults (>18 years) using the filled treatment, and no significant difference was observed in adolescents or young children (<18 years), which may be due to differences in the anatomy of the external auditory canal and autoimmunity between adults and adolescents. In addition,

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Table 3. Subgroup analysis of whether endoscopy was used

Outcome indicator	Subgroup	Number of studies included	Heterogeneity		Effect model	Outcome RR (95% CI)	Test for subgroup differences	
			I^2 (%)	*p*			*Q*	*p*
Clinical efficacy	Self-application	6	0	0.69	Fixed effect	1.18 (1.11–1.24)	0.42	0.52
	Endoscopic application	1	–	–	Fixed effect	1.25 (1.05–1.49)		
Adverse reaction	Self-application	3	7	0.34	Random effect	0.79 0.60–1.06)	9.41	<0.01
	Endoscopic application	1	–	–	Random effect	0.27 (0.15–0.51)		

RR = relative risk; CI = confidence interval; *Q* = *Q*-Test

Table 4. Sensitivity analysis

Outcome indicator	Before exclusion			After exclusion		
	RR	95% CI	RR	*p*	95% CI	*p*
Clinical efficacy	1.18	1.12–1.25	<0.001	1.17–1.21	1.11–1.23	<0.001
Relapse rate	0.29	0.18–0.47	<0.001	0.29–0.31	0.12–0.54	<0.001
Adverse reaction	0.61	0.34–1.12	0.11	0.51–0.79	0.24–1.45	0.04–0.28

RR = relative risk; CI = confidence interval

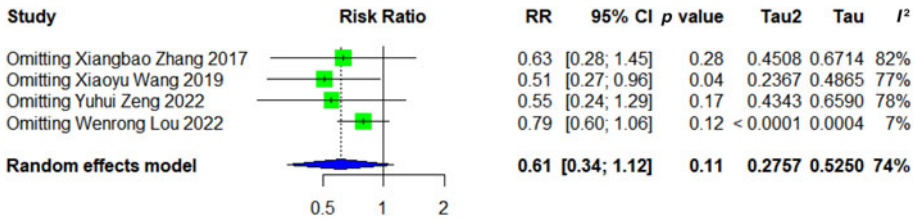

Figure 7. Adverse reactions with reversal. RR = relative risk; CI = confidence interval.

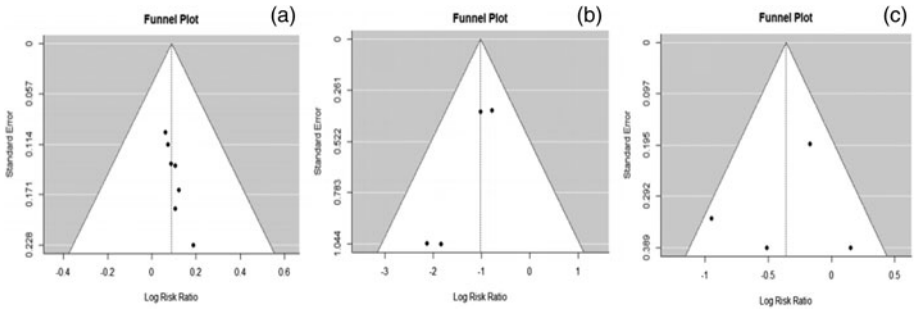

Figure 8. Publication bias: (a) clinical efficacy, (b) recurrence rates and (c) adverse reaction.

after finding that the adverse reaction results showed instability after excluding a particular study, and re-reading the full text did not reveal clinically or methodologically significant heterogeneity, the instability of the adverse reaction results may be due to sample size and data limitations, and the results need to be interpreted with caution.

This study is original in many ways and is the first meta-analysis of drug delivery modalities for fungal infections of the external auditory canal, filling a research gap in this area. The clinical outcomes of the two treatment modalities, filled and smearing, were compared and a number of key indicators, such as recurrence rate and adverse effects, were taken into account to provide a comprehensive assessment of treatment efficacy. This uniqueness and comprehensiveness added value to our study and it provides an important foundation for future research.

The results of the study also have direct practical application for clinicians and patients, helping them to make more informed treatment choices and improve patients' quality of life. The study helps to optimise the use of healthcare resources by reducing the burden on the healthcare system by reducing the number of medical visits and the cost of treatment through fewer recurrences. Most importantly, the study provides an important scientific basis for treatment guidelines for fungal infections of the

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external auditory canal, which is important for guiding future clinical practice and policy development. However, there are also some limitations to the study. Firstly, all included studies were from China and lacked multicentre, multinational data, thus this research may have limited applicability to other ethnic or geographic regions. Secondly, there is a paucity of relevant literature within the field, which makes it difficult to make direct comparisons with other studies, thus limiting a more in-depth exploration of the findings. Finally, in the subgroup analyses, the sample sizes for certain subgroups were small, which may have affected the stability of the results and limited a deeper understanding of subgroup differences.

- This meta-analysis compared the efficacy and safety of two modes of administration (external ear canal filling and smearing) for treating otomycosis, a common fungal infection of the ear
- A computerised search of databases was conducted and 7 studies with 934 patients were included
- The filled group (external ear canal filling) showed higher clinical efficacy and lower recurrence rates compared with the smear group (external ear canal smearing)
- There was no significant difference in adverse effects between the filled and smear groups
- Subgroup analysis suggested that the effectiveness of the filling treatment may be influenced by factors such as age, with adults experiencing lower recurrence rates than adolescents or young children

In summary, despite these limitations, we believe that this study provides valuable insights for future research in this area and provides a strong basis for further exploration of the modes of administration of medications for fungal infections of the external auditory canal.

Future research directions include conducting multicentre studies to validate the applicability of the results, initiating long-term outcome studies to assess the long-term impact of treatment modalities, conducting in-depth studies on patient adherence, exploring new therapeutic approaches, especially mechanism studies at the molecular level, as well as updating the relevant clinical guidelines to ensure that patients receive better treatment outcomes and quality of life. These directions will help expand knowledge in this field and improve treatment.

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