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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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Abstract

Objective. Objectively 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 CNKI, CBM, Web of Science, PubMed, EMbase, CochraneLibrary to include randomised controlled trials or clinically controlled trials on the same drug in different modes of administration for the treatment of otomycosis.

Results. A total of 7 studies with 934 patients were included. The filler group had a higher clinical efficiency (RR=1.18, 95% CI: 1.12 - 1.24, P<0.0001) and a lower recurrence rate (RR=0.29 ,95% CI: 0.18 - 0.47, P<0.0001) compared to the smear group, and there was no significant difference in the adverse effects (RR=0.61 , 95% CI: 0.34 - 1.12,P=0.11).

Conclusion. Current evidence suggests that the efficacy of the delivery modality of external auditory canal filling treatment is significantly better than external auditory canal smearing.

Keywords

Otomycosis; Therapy method; Meta-analysis; Clinical Efficacy

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Text

Introduction

Otomycosis is a common superficial fungal infection of the ear that accounts for approximately 10-20% 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/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 patient's ability to go about their daily lives and jobs. The most common way of treating the disease at the moment is cleaning 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 which are 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 like cotton swabs to apply the medication on the skin surface of the external ear canal. However, there hasn't been a thorough evaluation of how these two medication delivery methods compare as of yet. Therefore, to provide a demanding

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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

Computerized search of relevant published studies in databases such as CNKI, CBM, Web of Science, PubMed, EMbase, Cochrane Library, etc. Search for keywords such as otomycosis, otomycosis, fungi and RCT. The deadline for publication of all literature is August 2023, and there is no restriction on the language of publication. All studies 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 is:

('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)

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ligibility criteria and study selection

All research comparing the effects of external ear canal filling and smearing were searched for. The following standards were fulfilled by all studies to be included:

(1)The type of study was a randomized controlled trial.(2)Study population: Clinically diagnosed with otomycosis.[5](3)Treatment： Localized medication(The experimental group was filled with the drug and the control group was smeared with the same drug).

(4)Outcomes: patients' clinical effectiveness rate, recurrence rate and adverse effects (including ear itching, ear swelling, ear pain, etc.) after drug administration.

The following are the exclusion requirements：

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 tumors of the middle ear.(2)Surgical treatment or animal research.(3)Repeat study.(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 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 subsequently, valid data

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were extracted using an Excel spreadsheet, which was then cross-checked by another investigator.

Quality assessment

As the included literature were all RCTs, we were evaluated using the risk of bias assessment tool provided in the Cochrane Systematic Evaluator's Handbook 5.1.0,and plotted risk of bias using the robvis package of R 4.3.1 software. 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.And we settle our differences by discussing them with each other or by asking other authors for help.

Statistical analysis

Since the outcome indicators we chose were all dichotomous variables, the intervention effect was estimated by calculating the RELATIVE RISK (RR) and 95% confidence interval (CI).We statistically analyzed the raw data using the meta package of R 4.3.1 software.We used the Q-test to test for heterogeneity between studies. When the p-value of the Q-test[6] is more than 0.1 and the I^2 value is less than 50%, this means that the studies are homogeneous and we will choose the fixed effects model.However, if the p-value of the Q-test is less than or equal to 0.1 and the I^2 value is more than or equal to 50%, it indicates that there is heterogeneity among the studies, so we will use a random effects model. For possible heterogeneity, we will analyze according to predefined subgroups.We will perform sensitivity analysis to evaluate the stability and reliability of the Meta-analysis results and evaluate the publication bias of the included literature with the help of funnel plots.

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Results and analysis

Literature screening

According to the initially formulated strategy to retrieve articles: PubMed 21, EMBase 22, WebofScience 66, CBM 139, CochraneLibrary: 72, CNKI: 174, China Clinical Trial Registry 0, U.S. Clinical Trial Registry 10, a total of 504, removing duplicates of 160 articles. After removing the duplicates of 160 articles, 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, 7 RCTs were finally included, with 1 article in English and 6 in Chinese, and the process and results of the literature screening are shown in (Fig. 1).

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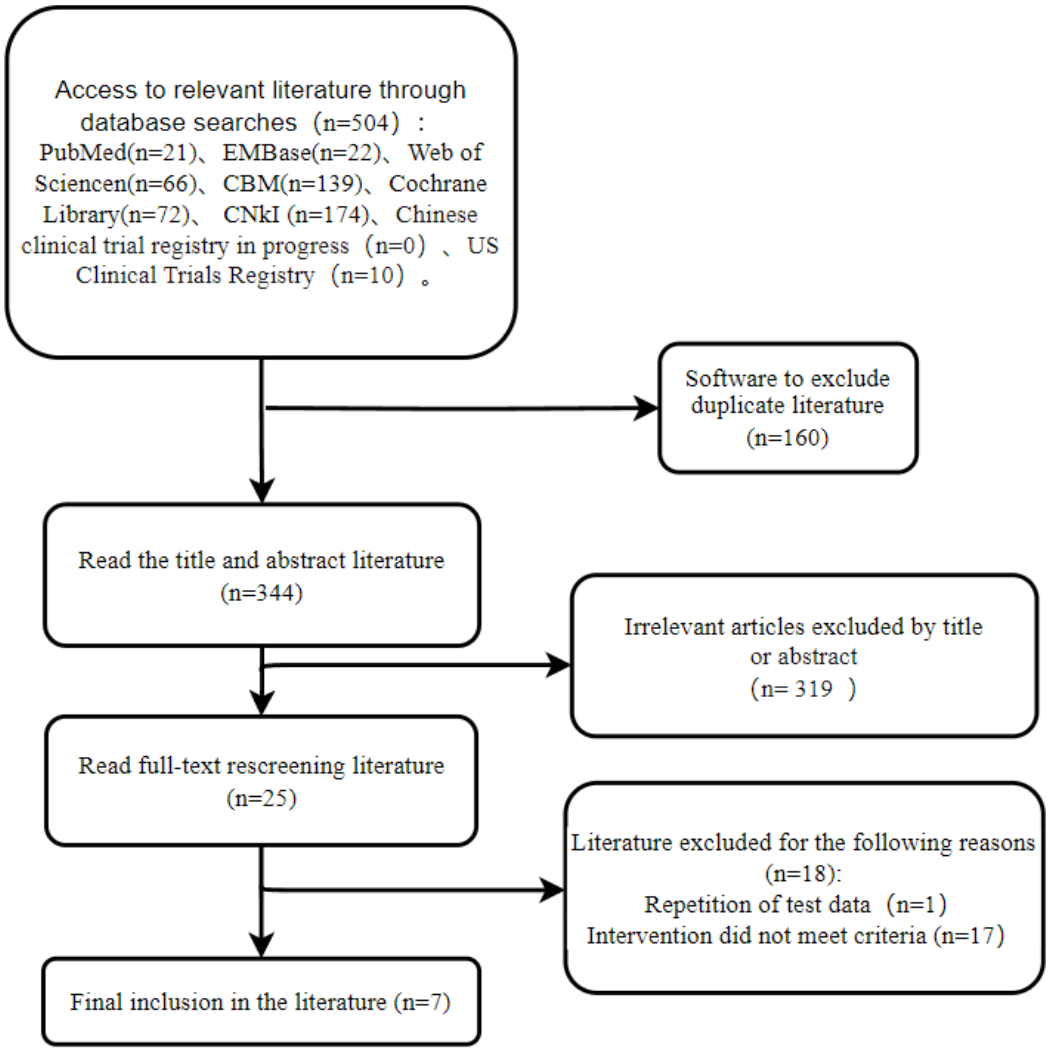

Fig. 1.Study flow chart.

Characteristics of inclusion studies

The seven studies we included were RCTs with a total of 934 patients. All 7 of these studies included the outcome metric clinical effectiveness, 4 studies included recurrence rates, and 4 studies included adverse events. One of the articles had a mean age of less than 18 years, and the other studies had a mean age of more than 18 years. The included articles described the

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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

We applied the Cochrane Handbook of Systematic Evaluation to evaluate the quality of the seven included literature. The evaluation results of the risk of bias evaluation of the included RCTs are shown in (Fig. 2 and Fig. 3).

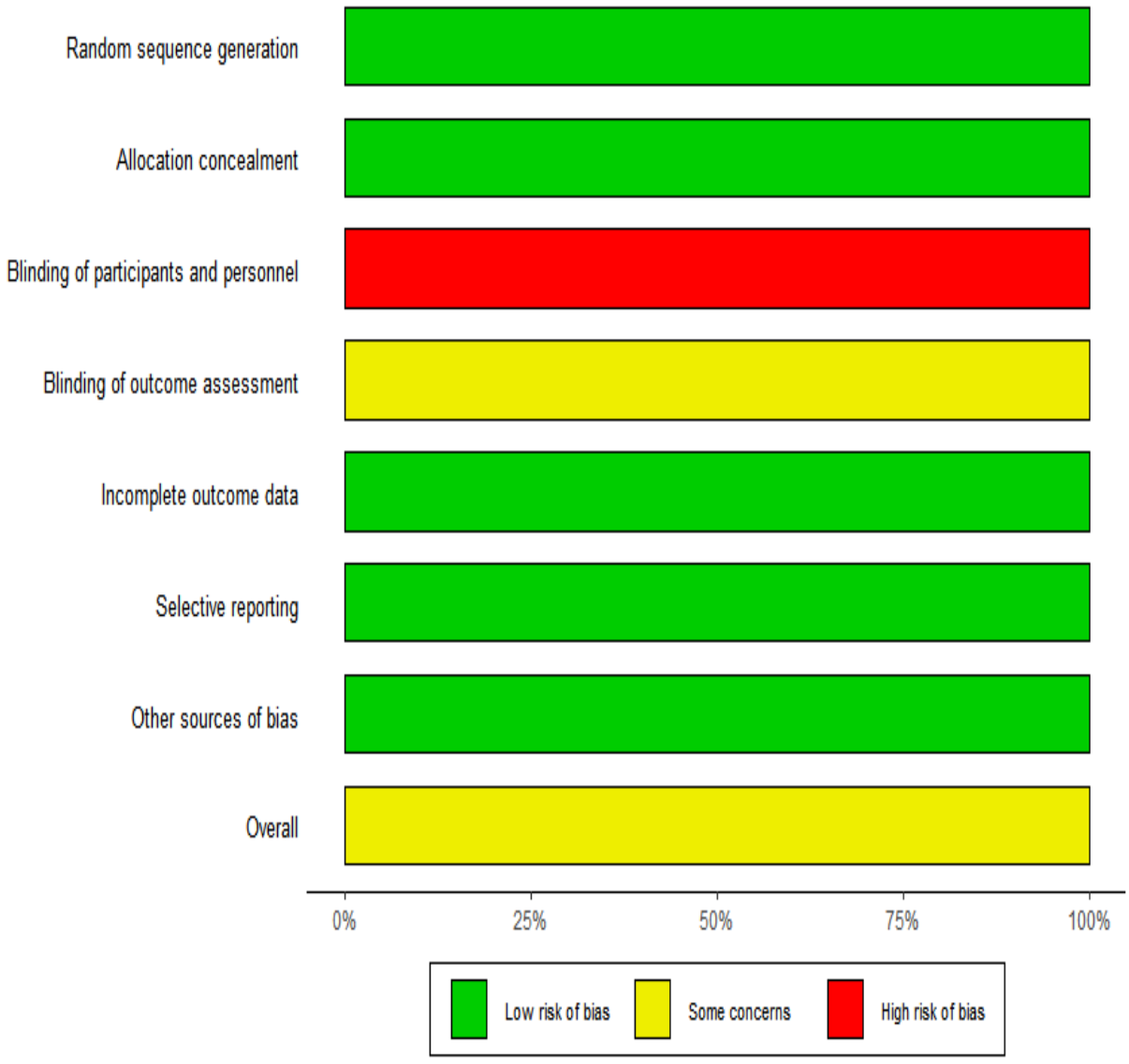

Fig. 2 Risk of bias graph

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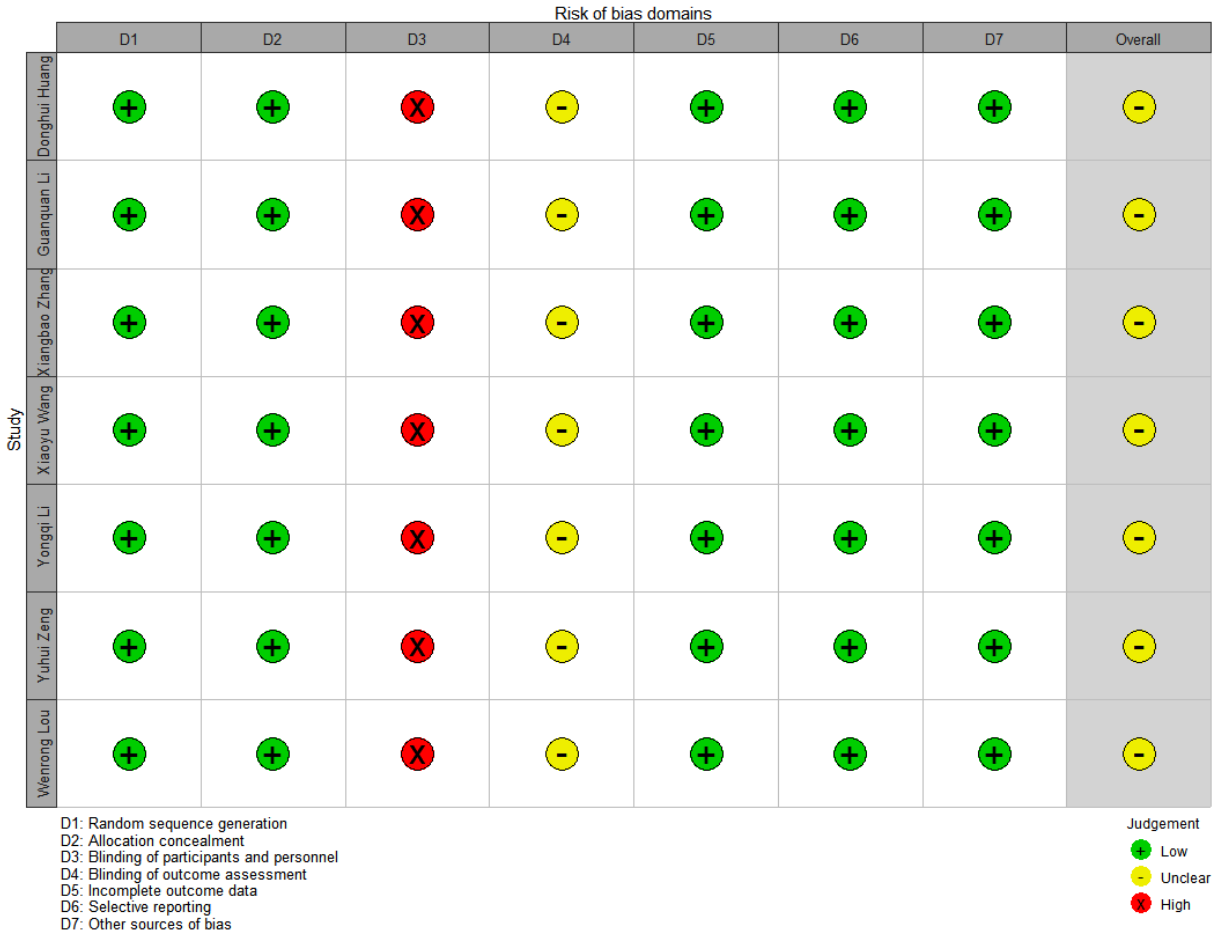

Fig. 3 Risk of bias summary

Outcomes

Clinical efficiency

The evaluation criteria were categorized as cured, apparent effect, effective and ineffective, and the total effective rate = (cured + apparent effect + effective) / total number of cases × 100%. 7 studies[7–13] of clinical efficacy, 934 patients were included, 510 in the experimental group and 424 in the control group, the forest plot is shown in (Fig. 4). The results of the heterogeneity test showed $I^2 = 0\%$, $P = 0.74$, indicating that there was no significant heterogeneity among the studies, so the fixed-effects model was used for Meta-analysis. The relative risk (RR) was 1.18 (95% confidence interval (CI): 1.12 - 1.24,$P < 0.0001$). Meta-

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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 filler group was significantly higher than that of the applicator group.

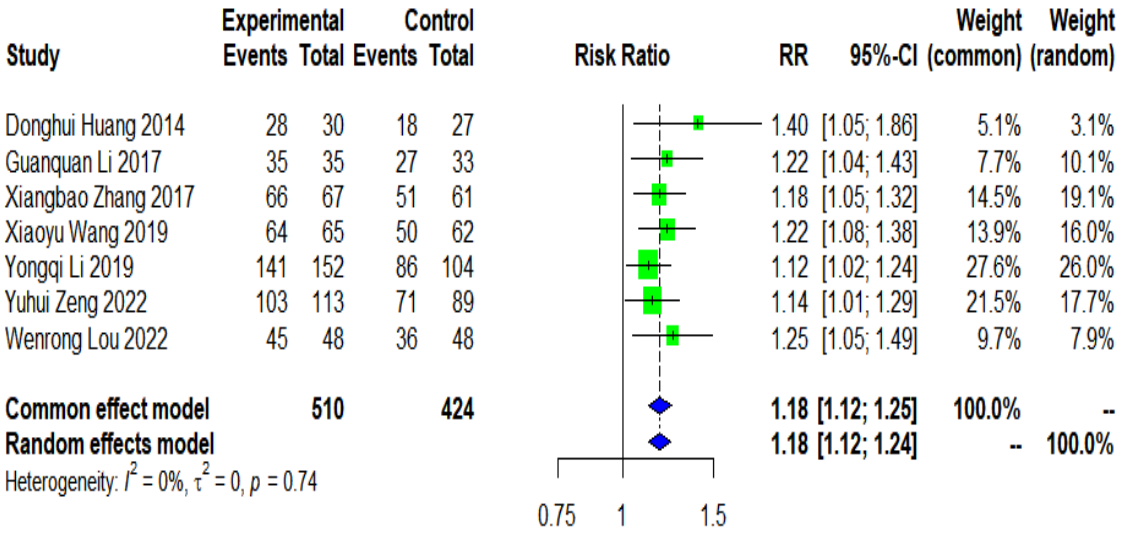

Fig. 4 Comparison of clinical effectiveness rates

recurrence rates

In the comparison of recurrence rates, 4 studies[8,10–12] were included with 627 patients, 352 in the experimental group and 274 in the control group, and the forest plot is shown in (Fig. 5). The results of the heterogeneity test showed that I^2 = 0%, P = 0.50, indicating that there was no significant heterogeneity among the studies, so the fixed-effects model was used for Meta-analysis.The relative risk (RR) was 0.29 (95% confidence interval (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 filler group was significantly lower than that in the applicator group.

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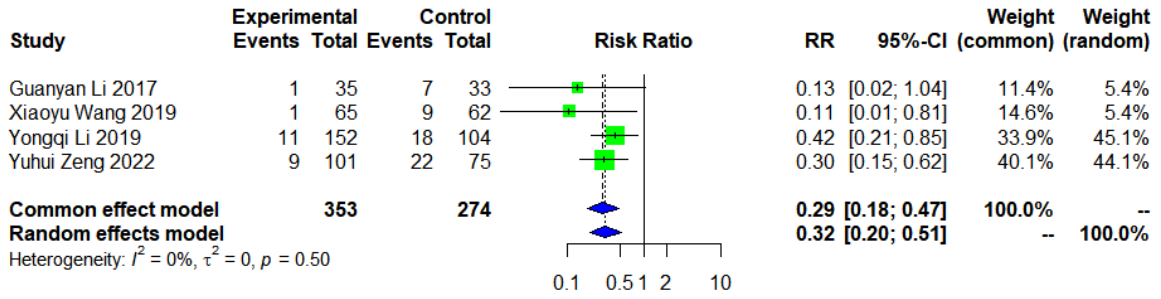

Fig. 5 Comparison of recurrence rates

adverse reaction

In the comparison of adverse reactions, 4 studies[9,10,12,13] were included 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= 74%, P < 0.01, suggesting that the heterogeneity between the literature selected for this study was statistically significant and that a search for heterogeneity needs to be performed.Meta-analysis was performed using a random effects model, and the RELATIVE RISK (RR) was 0.61 (95% confidence interval (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. The results showed that there was no difference in the incidence of adverse reactions between the filler and applicator groups.

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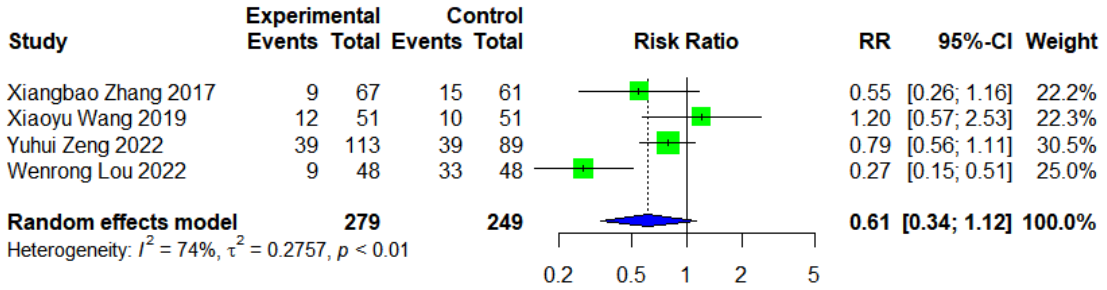

Fig. 6 Comparison of adverse reactions

Subgroup analysis

Subgroup analysis of mean age

Clinical effectiveness, recurrence rate, and adverse reactions were used as indicators, and the mean age was analyzed in subgroups with a cutoff of 18 years. Adverse reactions were dropped from this subgroup analysis because the mean age of 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 filler group compared to the applicator group (RR=1.18, 95% CI: 1.11- 1.25), the recurrence rate was significantly lower in the filler group compared to the applicator group (RR=0.31, 95% CI: 0.19- 0.51), and in the subgroup with mean age less than 18 years the filler group was significantly higher in the clinical effectiveness rate compared to the applicator group (RR= 1.22, 95% CI: 1.04- 1.43), and the recurrence rate in the filler group compared to the applicator group (RR=0.13, 95% CI: 0.02- 1.04) results were not statistically significant. The results are shown in Table 2.

Subgroup analysis of whether endoscopy was used

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Clinical effectiveness, recurrence rate, and adverse effects were used as indicators of clinical effectiveness and were categorized 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, in terms of clinical effectiveness: the filled group was significantly higher than the coated group (RR=1.18, 95% CI: 1.11- 1.24), and in terms of adverse effects: there was no statistically significant difference in the filled group compared to the coated group (RR=0.79, 95% CI: 0.60- 1.06). Among the subgroups of endoscopy, the filler group had a significantly higher clinical effectiveness rate than the applicator group (RR=1.25, 95% CI: 1.05- 1.49), and the filler group had significantly fewer adverse reactions than the applicator group (RR=0.27, 95% CI: 0.15- 0.51). This subgroup analysis resulted in a significant reduction in adverse reaction heterogeneity. The results are shown in Table 3.

Results of the sensitivity analysis

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 (Fig. 7).

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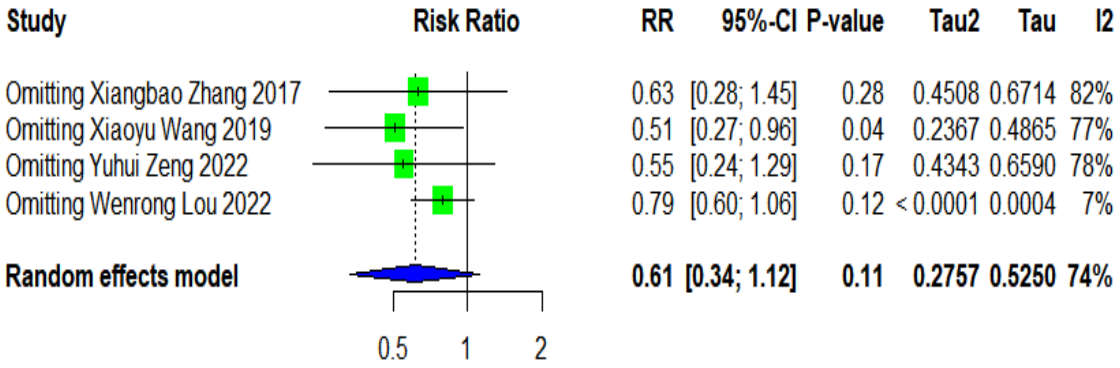

Fig. 7 adverse reactions with reversal

Publication bias analysis

A funnel plot with 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 detailed in (Fig. 8). The use of Egger's test was abandoned due to the inclusion of less than 10 studies[14]. Suggests that there may be publication bias in the selected literature.

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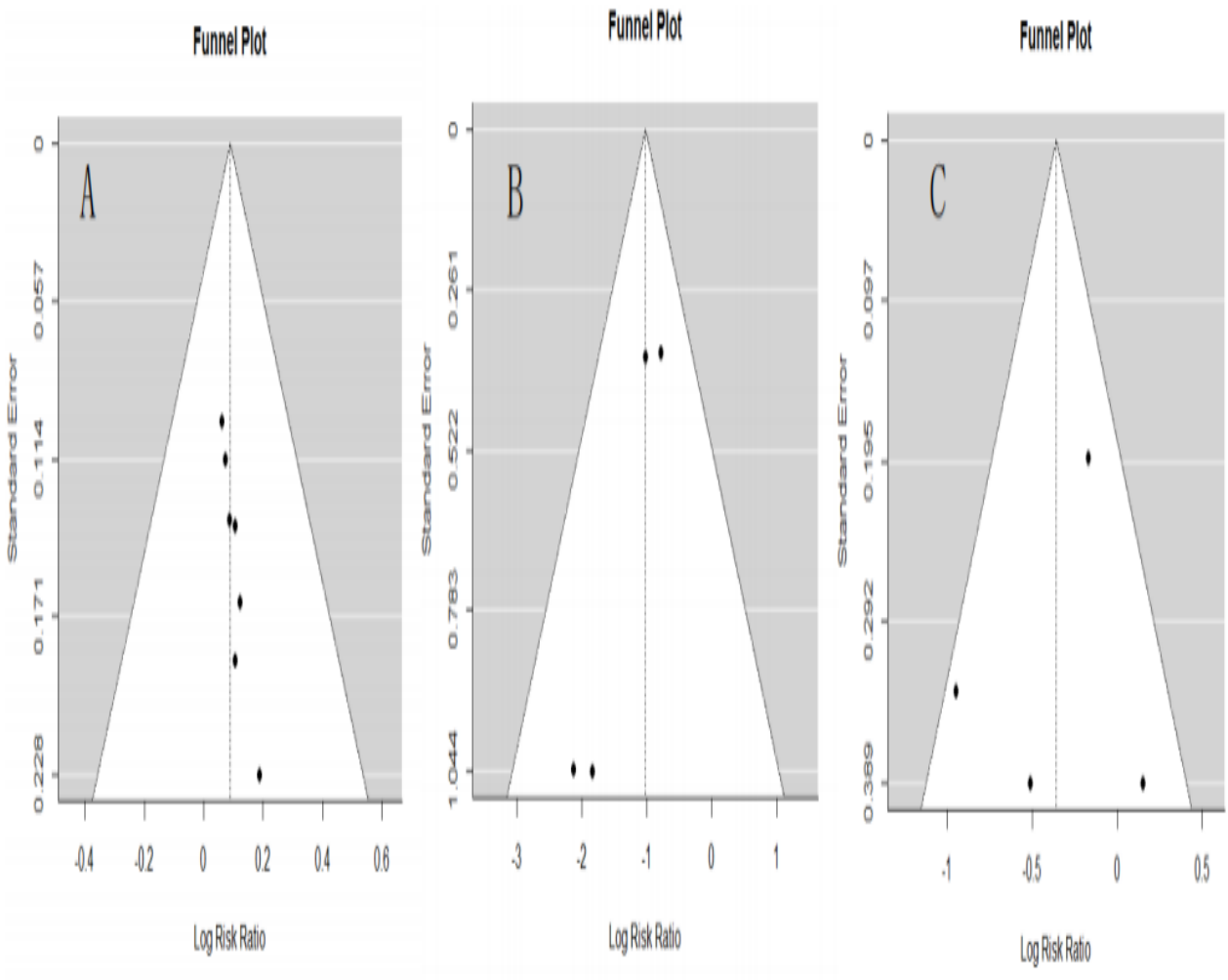

Fig. 8 Publication bias. A. Clinical efficiency; B. Recurrence rates; C. Adverse reaction.

Discussion

The aim of this study was to compare the efficacy and safety of the two main modes of administration (filling and smearing). PRINCIPAL FINDINGS: Our findings suggest that in the treatment of fungal infections of the external auditory canal, patients using filler 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

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was no significant difference between filler and applicator treatments in terms of adverse effects, and sensitivity analyses were not stable. In the subgroup analyses we also found that the factor of 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.

Explanations for why filler treatments perform better relative to smear treatments in fungal infections of the external auditory canal may include the following. (1) Increased area of drug contact: Filling therapy 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 fungus-infected area more efficiently to kill or inhibit the growth of the fungus. (2)Sustained efficacy: filler treatments usually require the medication to be retained in the external auditory canal for a period of time. Compared with smear treatments, the medication is contacted for a longer period of time and 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: Since application of treatment 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: patients' lifestyles and work schedules may not allow them to consistently apply the treatment on a daily basis, whereas filler treatments are easier to meet with 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. Some patients may not be able to apply

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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 in all subgroups, so application method may be the main reason for high heterogeneity of adverse reactions. In some studies9, it has been shown that the most common adverse effect is ear pain, which may be mainly 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) with filler 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, after finding that the adverse reaction results showed instability after excluding a particular study, and re-reading the go to full text did not reveal clinically or methodologically significant heterogeneity, then 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 multiple ways, and the first Meta-analysis of drug delivery modalities for fungal infections of the external auditory canal, filling a research gap in this area. We not only compared the clinical outcomes of the two treatment modalities, filler and applicator, but also took into account a number of key indicators, such as recurrence rate and adverse effects, to provide a more comprehensive assessment of treatment efficacy. This uniqueness and comprehensiveness adds value to our study and provides an important foundation for future research. In addition, the results of the study have direct practical application for clinicians and patients, helping them to make more informed treatment choices

and improve patients' quality of life. Also, our study helps to optimize the use of healthcare resources by reducing the burden on the healthcare system by decreasing the number of medical visits and the cost of treatment through fewer recurrences. Most importantly, this study provides an important scientific basis for treatment guidelines for fungal infections of the external auditory canal, which is important for guiding future clinical practice and policy development. However, we must also recognize some limitations of the studies. First, all included studies were from China and lacked multicenter, multinational data, and thus 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. 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 multicenter 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 the field and improve treatment.

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References

1 Tasić-Otašević S, Golubović M, Đenić S, Ignjatović A, Stalević M, Momčilović S, et al. Species distribution patterns and epidemiological characteristics of otomycosis in Southeastern Serbia. J Mycol Med 2020;30(3):101011

2 Ho T, Vrabec JT, Yoo D, Coker NJ. Otomycosis: Clinical features and treatment implications. Otolaryngology–Head and Neck Surgery 2006;135(5):787–791

3 Chen Q, Chu H, Tao Y, Peng L, Zhou L, Liu L, et al. A Comparison of Triamcinolone Acetonide Econazole Cream and Nystatin Suspension in Treatment of Otomycosis. Laryngoscope 2021;131(5):E1640-E1646

4 Koltsidopoulos P, Skoulakis C. Otomycosis With Tympanic Membrane Perforation: A Review of the Literature. Ear Nose Throat J 2020;99(8):518-521

5 Alarid-Coronel J, Celis-Aguilar E, Escobar-Aispuro L, Muñoz-Estrada V. Otomycosis in immunocompetent patients: Clinical and mycological features. Our experience with 40 cases. Clin Otolaryngol 2018;43(1):373–7

6 Stogiannis D, Siannis F, Androulakis E. Heterogeneity in meta-analysis: a comprehensive overview. The International Journal of Biostatistics 2023 Mar 27

7 Huang DH, Ji SF, Chen JX, Chen XH. Clinical observation of different modes of administration of mycotoxin cream in the treatment of fungal otitis externa. China Pharmacy 2014;(16 vo 25):1467–8

8 Li GY, Xu DY, Li CL, Zhao FL. Preliminary study on the clinical efficacy of otoscopic cleaning combined with parexone external auditory canal irrigation for the treatment of

fungal disease of the external auditory canal in children. Chinese Medical Science 2017;(10 vo 7):217–9

9 Zhang XB, Hu BH. Observation on the efficacy of injecting Parasone ointment into the external auditory canal for the treatment of fungal otitis externa. Chinese Journal of Integrative Otolaryngology 2017;25(1):26-29,8

10 Wang XY, Kong DJ, Zhang ZD. Effects of different administration modes of Parasone ointment on the efficacy of fungal otitis externa and serum inflammatory factor. China Exploration of Rational Drug Use 2019;(9):149-151,154

11 Li Y, He L. Diagnosis and treatment of otomycosis in southern China. Mycoses 2019;62(11):1064–8

12 Zeng YH, Hu ZY, Lin HL, Cai WW, Huang YL. Analysis of the efficacy of parresone in fungal external otitis. Chinese Journal of Endoscopy 2022;28(2):56–62

13 Lou WR, Zhou Z, Liu J. Efficacy of ear endoscopic drug tamponade in treating mycosis of the external auditory canal. Practical medicine in China 2022;(10 vo 17):110–2

14 Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. British Medical Journal 2011;343:d4002

Tables and Charts

Table 1. Characteristics of the Included Literature

First Author	Years	Study Design	Sample size（T/C)	Male/Female	Average age (years)	Medicines	Interventions		Outcomes	Intervention Duration
							t	c		
Donghui Huang	2014	RCT	30/27	35/22	32.62 ±5.8	Nystatin Cream	Filling	Smearing	①	2w
Guanquan Li	2017	RCT	30/30	36/24	5.4± 1.45	Triamcinolone Acetonide and Econazole Nitrate Cream	Filling	Smearing	①②	10-14d
Xiangbao Zhang	2017	RCT	43/38	38/43	35.38 ±1.20	Triamcinolone Acetonide and Econazole Nitrate Cream	Filling	Smearing	① ③	2w
Xiaoyu Wang	2019	RCT	51/51	63/39	37.19 ± 11.31	Triamcinolone Acetonide and Econazole Nitrate Cream	Filling	Smearing	①②③	2w
Yongqi Li	2019	RCT	152/104	133/123	35.1	Triamcinolone Acetonide and Clotrimazole Cream	Filling	Smearing	①②	2-3w
Yuhui Zeng	2022	RCT	113/89	97/105	36.63 ± 14.64	Triamcinolone Acetonide and Econazole Nitrate Cream	Filling	Smearing	①②③	1w
Wenrong Lou	2022	RCT	48/48	55/41	46.7± 9.8	Triamcinolone Acetonide and Econazole Nitrate Cream	Filling	Smearing	① ③	2w

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Note:①:Clinical efficiency；②:recurrence rates；③:adverse reaction

Table 2. Subgroup analysis of mean age

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

Table 3. Subgroup analysis of whether endoscopy was used

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

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Table 4 Sensitivity analysis

Outcome indicator	Before exclusion		After exclusion			
	RR	95%CI	RR	P	95%CI	P
Clinical efficiency	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

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Bullet Point Summary

- The 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 computerized search of databases was conducted, and seven studies with 934 patients were included in the analysis.
- The filler group, which involved external ear canal filling, showed higher clinical efficiency and lower recurrence rates compared to the smear group (external ear canal smearing).
- There was no significant difference in adverse effects between the filler and smear groups.
- Subgroup analysis suggested that the effectiveness of filling treatment may be influenced by factors such as age, with adults experiencing lower recurrence rates than adolescents or young children.

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