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**Different medications for the treatment of Ménière's disease by
intratympanic injection:
a systematic review and network meta-analysis**

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Abstract

Background: It is generally accepted that intratympanic injection provides an effective approach to manage severe vertigo in Ménière's disease. Although there are several medications available, that which is the most effective is still subject to debate.

Objective: To assess the effectiveness and safety of the different medications used in treatment of Ménière's disease by intratympanic injection using a network meta-analysis.

Methods: PubMed, EMBASE, CINAHL and CENTRAL were searched. Only randomized controlled trials that compared the effectiveness of medications used for intratympanic injection to treat Ménière's disease with each other or a placebo were included. The primary outcome assessed was the effectiveness of medication in the management of vertigo

symptoms. The effectiveness was expressed in terms of risk ratio (RR) with a 95% credible interval (CrI) for individual studies analyzed. Network meta-analysis was performed by Stata version 15.0 using the network package.

Results: Nine studies involving 314 patients treated with 5 different medications were included in the present analysis. Number of injections given varied from 1 to 10 and follow-up time from 3 to 28 months. When compared to each other or to a placebo, Gentamicin was found to be the most efficacious medication, followed by Methylprednisolone, Latanoprost, Dexamethasone and Ganciclovir in order of effectiveness. However, no significant difference in efficacy was found between Gentamicin and Methylprednisolone when outcomes from studies with a follow-up time equal to or more than 24 months were analyzed. It was not possible to conduct subgroup and sensitivity analysis because of the limited number of studies that were included.

Conclusion: All medications are more effective than a placebo in the treatment of Ménière's disease by intratympanic injection. According to the SUCRA, Gentamicin ranked the most effective, with Gentamicin and Methylprednisolone equally effective in the long-term. When the potential risk of hearing loss induced by Gentamicin is taken into consideration, Methylprednisolone may be the best choice for treatment of Ménière's disease by intratympanic injection.

Key points:

- There is currently no consistent guidance as to the most effective method to treat Ménière's disease, however, it is generally accepted that intratympanic injection provides an effective way to manage severe vertigo in the acute phase of repeated attack.
- This network meta-analysis shows that all medications are more effective than a placebo for the treatment of Ménière's disease by intratympanic injection. According to the SUCRA, Gentamicin ranked as the most effective with the efficacy of Gentamicin and Methylprednisolone similar in terms of their long-term effect.
- Considering the potential risk of hearing loss induced by Gentamicin, Methylprednisolone may be the best choice for intratympanic injection for Ménière's disease.

1. Introduction

Ménière's disease is a common disorder characterized by recurrent episodes of spontaneous vertigo, fluctuating hearing loss and tinnitus, often with a feeling of fullness in the ear. Because of different diagnostic criteria, especially in the early stages, prevalence figures differ widely from 10 to 513 per 100,000 population.¹⁻⁶ A number of important aetiological factors have been implicated in the development of Ménière's disease such as; stress, dyssomnia, allergies, immune dysfunction, autonomic dysfunction, poor mental health, and even atmospheric pressure.⁷⁻¹⁰ Symptoms associated with Ménière's disease also occur in up to 20% of family members, indicating a strong genetic influence.¹¹

The pathophysiology underlying Meniere's disease is suggested as endolymphatic hydrops,¹² most likely due to an abnormality in the absorption of endolymph at the endolymphatic sac,¹³ a hypoplasia of the vestibular aqueduct,¹⁴ a genetic predisposition to anatomic abnormality¹⁵ or a reactivation of latent herpes simplex virus¹⁶. However, the precise cause of the hydrops remains uncertain.¹⁷

Ménière's disease has a considerable effect on a person's quality of life, as a result of its symptoms. The primary aim of treatment however is to reduce the number of episodes and severity of vertigo. Amelioration of aural symptoms (e.g., hearing loss, aural pressure and tinnitus) is also taken into consideration by clinicians. Efficient and specific treatment options are limited at present. For example, the study by Manzoor et al.¹⁸ suggests that Ménière's disease is a multifactorial disorder and no single treatment can provide relief in all patients at the initial phase of the disease. Currently it is generally accepted that intratympanic injection provides an effective way to manage severe vertigo¹⁹ in the acute phase where there are repeated episodes.

Two Cochrane systematic reviews by Phillips et al.²⁰ and Pullens et al.²¹ assessed the effectiveness of intratympanic injections in the treatment of vertigo in Ménière's disease. Although their conclusion suggests that intratympanic injection of either gentamicin or steroid appears effective, this work requires updating to include several new clinical trials.^{22,23} Moreover, there is an urgent need for a better understanding of the specific benefits and shortcomings of

individual medications by direct comparisons. This would contribute greatly to the development of more clear clinical guidance on medications used for the management of Ménière's disease using intratympanic injection.

The purpose of this systematic review is to assess the effectiveness and safety of different medications used in intratympanic injection for Ménière's disease by a network meta-analysis. Network meta-analysis is a statistical tool that enables information from different trials that address the same variables but using different interventions to be analyzed. It has been used to compare different treatments with each other and with a placebo, allowing direct and indirect comparison between these different interventions. To the best of our knowledge, this is the first network meta-analysis to address the efficacy of different medications used in intratympanic injection for Ménière's disease.

This review has been registered in PROSPERO (CRD: 42018115292).

2. Methods

2.1 Criteria for study consideration

2.1.1 Types of studies

Only randomized controlled trials (RCTs) were included in this systematic review.

2.1.2 Characteristics of participants

All patients diagnosed with Ménière's disease according to the diagnostic guidelines of the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) in 1995²⁴ were included.

2.1.3 Types of interventions

All studies that described the effectiveness of a medication, when compared to a placebo, in intratympanic injection were included. We also included studies that provided direct comparison of the effectiveness of medications used in intratympanic injection.

2.2 Types of outcome measures

Effectiveness of vertigo symptom management was used as the primary outcome as suggested by the AAO-HNS 1995. In addition, other outcomes were considered, including changes to hearing thresholds, severity of tinnitus, felling of aural fullness and adverse effects.

2.3 Search strategy for identifying studies

2.3.1 Electronic database searches

The database of PubMed, EMBASE, CINAHL and CENTRAL were searched.

We used combined terms of Medical Subject Headings (MeSH), keywords or free text words to model search strategies and the search strategies were adapted to the requirements of each database.

2.3.2 Searching other resources

In addition, manual searches were made for relevant references from identified publications as well as abstracts from scientific meetings over the last five years from relevant groups (e.g., British Society of Audiology, Bárány Society, European Academy of Otolology and Neurotology (EAONO), American Academy of Otolaryngology-Head and Neck Surgery (AAO--HNS), Japan Society for Equilibrium Research and Korean Balance Society) to avoid searching bias.

2.4 Data collection and analysis

2.4.1 Selection of studies

Two authors (ZC, FY) independently examined the titles and abstracts of studies identified using the search strategy mentioned above to check relevance. After reviewing the full text of articles, relevant studies were identified and included as eligible studies based on the inclusion criteria. Any disagreements that could

not be solved after discussion, led to arbitration provided by one of the other authors (FZ, WH).

2.4.2 Data extraction and management

Two authors (ZC, WH) independently used an agreed data collection form to extract data from the included studies. Data extracted was double checked for accuracy, and any disagreements after discussion arbitrated by one of the other authors (FZ, FY). Attempts were made to contact the corresponding authors for additional information on outcomes that were needed but not reported in the studies.

2.5 Assessment of risk of bias in included studies

Two authors (FY, WH) independently followed the guidance in the Cochrane Handbook for Systematic Reviews of Interventions²⁵ to assess risk of bias in the included studies. Any disagreements after discussion was arbitrated by one of the other authors (FZ, ZC).

2.6 Ethical considerations

No ethical approvals were required for this review as no patients and public were directly involved.

3. Data analysis

We expressed medication effectiveness in terms of risk ratio (RR) with a 95% credible interval (CrI) for individual studies with count outcomes, e.g. the number of patients with no vertigo complaints after treatment. Network meta-analysis with a consistency model was undertaken to compare different medications for intratympanic injection for Ménière's disease. A network plot obtained from Stata software was used to ensure that trials were connected by interventions and any trials that were not connected were excluded. To assess inconsistency,^{26,27} inconsistency factor (IF) plots created by Stata software were used. The ranking probabilities for all interventions was estimated.

The surface under the cumulative ranking curve (SUCRA) (cumulative probability) and relative ranking table with CrI for the ranking probabilities was calculated.^{27,28} Sensitivity analysis was gained by excluding studies at high risk of bias to assess the robustness of the analyses. Subgroup analysis was also conducted according to the type of medication and follow-up time. Possible presence of publication bias or small-study bias was checked for using funnel plots. All analyses were performed with Stata version 15.0 using the network package.²⁹

3. Results

3.1 Studies retrieved and summary

537 studies were identified by the literature search strategies. Of these, 116 studies were duplicates. From the remainder, 367 were removed after screening titles and abstracts. Full texts of 54 records were read to assess their eligibility, 11 were considered. Of these, 2 were excluded because they described clinical trials of OTO-104, which is not available clinically. Although several ongoing studies were identified, unfortunately no detailed information was disclosed by the authors for further analysis. As a result, nine studies were eventually included in the present analysis. Figure 1 shows the study selection process in a PRISMA flow diagram.

Table 1 summarises the characteristics of the included studies for the network meta-analysis. The 9 studies were published between 2004 and 2017, and a total of 314 patients participated in these studies, which were conducted in seven countries. Among these studies, five individual medications were used for intratympanic injection for Ménière's disease. They were Gentamicin, Dexamethasone, Methylprednisolone, Ganciclovir and Latanoprost. Of these, Gentamicin was the most commonly used. Three studies³⁰⁻³² compared the effectiveness between Gentamicin and placebo, whilst a further 3 studies³³⁻³⁵ compared the effectiveness of Gentamicin, Dexamethasone and Methylprednisolone to each other. There was only one study each that looked at

the effectiveness of Dexamethasone, Ganciclovir and Latanoprost against a placebo.

The number of injections given varied from 1 to 10 and follow-up time varied between 3 and 28 months for all included studies except that of Rask-Andersen et al.³⁶, which revealed outcomes at 2 weeks after injection only. In the 2 studies^{33,37} where results were measured at different follow-up times, the results from the last measurement was used for analysis, as recommended by AAO-HNS.

All of the included studies reported the primary outcome, i.e., the effectiveness of vertigo symptom management. Four^{32,33,35,38} reported outcomes in terms of vertigo numeric scale value based on AAO-HNS criteria, four^{30,31,34,37} reported the number of patients with no vertigo complaints, whilst the last study³⁶ only presented the individual VAS scores of vertigo in their figures, from which can identify how many patients experienced significant improvement. The other outcomes assessing vertigo, such as DHI, VSS or SI scores, were reported only by two studies.^{34,39} In this situation, effect was expressed in terms of risk ratio (RR) with 95% credible interval (CrI) for the primary outcome analysis. However, due to limited information on other outcomes, no further analysis was conducted on hearing loss, tinnitus, aural fullness and other adverse events.

As shown in Figure 2, the overall quality of studies in GRADE assessment was moderate. Only one trial³⁴ was judged to have no risk of bias, two studies^{31,33} were judged high risk and the others moderate risk. Most had evidence of high risk or unclear risk of bias in terms of the random sequence generation as only 3 studies^{32,34,37} clearly described their random sequence generation procedures. There was also other bias in one trial as they did not finish their study.

Network graphs of all the eligible comparisons for the primary outcomes are presented in Figure 3. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the sample size. There are more trials and patients comparing gentamicin to placebo and two loops in which each medication has direct trial comparisons with at least two other medications. A global inconsistency test was then performed in the loops shown in Figure 4, which suggested no evidence of inconsistency of treatments for the primary outcomes.

Pairwise comparison is presented in a league table as shown in Table 2. The surface under the cumulative ranking curve (SUCRA) is shown in Table 3. In all of the included studies, there was high-certainty of evidence of benefit for all medications when compared to placebo. The rankograms showed Gentamicin as the most efficacious medication when compared to the others, followed by Methylprednisolone, Latanoprost, Dexamethasone and Ganciclovir. It was not

possible to conduct subgroup and sensitivity analysis because of the limited number of included studies. However, no significant difference was found between Gentamicin and Methylprednisolone in terms of efficacy when the outcomes obtained from studies having follow-up times equal to or more than 24 months were used (Table 4). In respect of the safety of these medications, especially the effect on hearing, no definite conclusions can be drawn due to the lack of data in the included studies. The funnel plot in Figure 5 suggests that the current results might be influenced by the sample size of literature and publication bias.

4. Discussion

Although the present review shows that all medications are more effective than placebo for the treatment of Ménière's disease, the included medications were not equivalent, according to the SUCRA. Gentamicin ranked as the most effective with Methylprednisolone ranked second, followed by Latanoprost, Dexamethasone and Ganciclovir in that order. However, caution is needed to interpret the effectiveness of Latanoprost as results were obtained from the only study using Latanoprost that recruited only 9 patients even though a placebo-controlled double-blind study design was adopted in that trial. In addition, since Ménière's disease is a chronic illness and also a fluctuating disease with a strong placebo effect, it is suggested that attention should be paid to the long-term efficacy of treatments. When literature with less than 24

months' follow-up time was excluded, the efficacy of Gentamicin and Methylprednisolone were similar.

The most common and effective intratympanic injection medication used in the treatment of Ménière's disease so far is Gentamicin. However, Gentamicin has an ototoxic effect that causes direct damage to the sensorineural epithelium and hair cells of the labyrinth, and thereby affects vestibular and cochlear function.⁴⁰

Although use of Gentamicin has become increasingly popular since its introduction in 1981,⁴¹ the risk of damaging cochlear function has led to the adoption of a variety of injection dosing schedules and treatment duration to minimize risk. There remains no current consensus on clinical guidelines for the use of Gentamicin in terms of dose and duration.^{42,43} The alternative approach of using steroids has been suggested as a better option due to its immunoregulatory function and anti-inflammatory effects and the absence of severe side effects on inner ear function. Several prospective, randomized, double-blind, placebo controlled studies compared steroid use (i.e., Dexamethasone, 4 mg/ml³⁸ or OTO-104, 60 mg/ml²²) versus placebo with inner ear perfusion. The results showed that steroids provided better intervention in terms of managing the vertigo symptoms.

Furthermore, Patel³⁴ compared the effectiveness of Methylprednisolone (62.5mg/mL) with Gentamicin and no significant difference was seen in controlling vertigo. Other studies have however shown negative results when the effect of the Dexamethasone (4 mg/ml) was compared to Gentamicin.^{44,45}

Such inconsistent conclusions are likely to be due to different study designs, e.g., type and dose of the steroids such as Methylprednisolone, OTO-104 and Dexamethasone. The findings of this network meta-analysis suggest that Gentamicin is the most effective medication for intratympanic injection for Ménière's disease. However, considering the substantial risk of hearing loss induced by Gentamicin, Methylprednisolone may be the more efficacious choice.

The strengths of this review are that a complex network meta-analysis was performed to compare the efficacy of all available medications for intratympanic injection for Ménière's disease in order to identify the best treatment. Multiple databases and reference lists were searched to identify as many relevant studies as possible. All the relevant studies were randomized controlled trials as these can avoid most kinds of bias in the design and implementation and strengthen the quality of analysis. Study selection, data extraction and quality assessment were also undertaken by two independent researchers with a high level of agreement to avoid selection bias.

However, our review needs to be viewed in light of several limitations. Firstly, the outcomes derived from this review are certainly affected by the shortcomings of the included studies. There are several limitations in some of the included studies, such as too small a sample size to support strong external validity (the funnel plot indicates that our conclusion may be influenced by small sample size literature. For example, as mentioned above, Latanoprost may

not be as effective as suggested because only 9 patients were recruited in that trial.), inappropriate study design in terms of blinding, e.g. did not adopt a double-blind trial, and many of the trials had a short duration of follow-up time (the shortest follow-up time was only 2 weeks) given that Ménière is a chronic disease. Secondly, when planning this review, we aimed to include ongoing trials and indeed a number were researched, unfortunately, we had to give up these studies because the researchers did not reply to us with details requested. There may be some English language bias as well as only English literature was included. The last but most important limitation of this review is that we only analyzed the primary outcome and not the other outcomes, especially the unwanted hearing loss. There was substantial variation across the included studies in terms of outcomes assessed. Some studies used continuous variables, e.g., the mean increase in PTA, to assess the outcomes, whilst others used count outcomes, e.g., the number of patients that the hearing improved. It is not possible to analyze as the data types are not uniform. Future researchers should consider these outcomes and other adverse events rather than only vertigo management.

5. Conclusion

All medications are more effective than a placebo in the treatment of Ménière's disease by intratympanic injection. According to SUCRA, Gentamicin ranked the most effective, followed by Methylprednisolone, Latanoprost,

Dexamethasone, and Ganciclovir in that order. The efficacy of Gentamicin and Methylprednisolone are similar in terms of their long-term effect. Considering the potential risk of hearing loss induced by Gentamicin, Methylprednisolone may be the best choice for intratympanic injection for Ménière's disease. It is noteworthy that the effectiveness of Latanoprost needs to be interpreted cautiously due to its small sample size, even though a placebo-controlled double-blind study design was adopted. In future studies, more large-sample size and multi-center RCTs should be carried out to further validate the effectiveness of intratympanic injection for the treatment of Ménière's disease.

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Table 1 A summary of characteristics of included studies for the network meta-analysis.

Study	Sample		Treatment			Follow-up time (month)	Outcome							
	T	C	Drug		Total injections		Vertigo		Hearing loss		Tinnitus		Aural fullness	
			T	C			T	C	T	C	T	C	T	C
Anaya et al. (2005), Mexico	1	7	De	Pla	5	24	Class A and B of vertigo control: 11	Class A and B of vertigo control: 4	Mean increase in PTA: -2.2	Mean increase in PTA: -0.5	Mean decrease in THI: 38.7	Mean decrease in THI: 41.2	NA	NA
Bremer et al. (2014), Netherlands	5	5	Ge	Pla	4	24	Class A and B of vertigo control: 4	Class A and B of vertigo control: 5	Mean increase in PTA: 27.4	Mean increase in PTA: 10	NA	NA	NA	NA
Casani et al. (2012), Italy	3	2	Ge	De	1-2/3	1/12/2	Class A and B of vertigo control: 30	Class A and B of vertigo control: 17	Mean increase in PTA: 5.8	Mean increase in PTA: -0.5	NA	NA	NA	NA
Guyot et al. (2008), Switzerland	1	1	Ga	Pla	10	1/2/3	Control of vertigo: 11	Control of vertigo: 11	NA	NA	NA	NA	NA	NA
Masoumi et al. (2017), Iran	3	3	De	MP	3	6	Class A and B of vertigo control: 25	Class A and B of vertigo control: 24	Improved: 4	Improved: 20	NA	NA	NA	NA

Patel et al. (2016), UK	3 0	3 0	MP n	Ge n	2	24	No vertigo complaints: 20	No vertigo complaints: 19	Mean increase in PTA: -2.1	Mean increase in PTA: -6.4	Mean decrease in THI: 19.8	Mean decrease in THI: 21.3	Mean decrease in AFS: 2.9	Mean decrease in AFS: 3.5
Postema et al. (2008), Netherlands	1 6	1 2	Ge n	Pla	4	12	No vertigo complaints: 9	No vertigo complaints: 0	Mean increase in PTA: 8.1(±18.1)	Mean increase in PTA: 0 (±0.7)	No significant change in TSS	No significant change in TSS	Significant lower in FSS	No significan t change in FSS
Rask-Andersen et al. (2005), Sweden	9	9	Lat	Pla	6	0.5	Significant reduction of vertigo in VAS: 6	Significant reduction of vertigo in VAS: 2	NA	NA	NA	NA	NA	NA
Stokroos et al. (2004), Netherlands	1 2	1 0	Ge n	Pla	1.5± 0.51	6-28	No vertigo complaints: 12	No vertigo complaints: 1	Mean increase in PTA: -6	Mean increase in PTA: 5.8	NA	NA	NA	NA

T: Treated group, C: Control group

Dex: Dexamethasone, Pla: Placebo, Lat: Latanoprost, Gen: Gentamicin, Gan: Ganciclovir, MP: Methylprednisolone

NA: Not Available

Class (A-F): Class of vertigo control according to the AAO-HNS committee classification, VAS: Visual Analogue Scale scores (0-100), PTA: Pure Tone Average (dB), THI: Tinnitus

Handicap Inventory scores, TSS: Tinnitus Severity scores, AFS: Aural Fullness Scale scores, FSS: Fullness Severity Scores

Table 2 League table of pairwise comparisons of treatment medications in the network meta-analysis

Pla					
-2.49 (-5.91,0.93)	MP				
-1.95(-5.85,1.96)	0.54(-4.65,5.74)	Lat			
-2.85		-0.90			
(-5.25,-0.45)	-0.36 (-3.12,2.41)	(-5.49,3.68)	Gen		
		1.66	2.56		
-0.29 (-4.00,3.43)	2.20 (-2.85,7.25)	(-3.73,7.05)	(-1.86,6.98)	Gan	
		0.12	1.02	-1.54	
-1.83 (-4.82,1.17)	0.66 (-2.10,3.43)	(-4.80,5.04)	(-1.56,3.60)	(-6.31,3.23)	Dex

Pla: Placebo, MP: Methylprednisolone, Lat: Latanoprost, Gen: Gentamicin, Gan: Ganciclovir, Dex: Dexamethasone

Table 3 Effectiveness ranking by surface under cumulative ranking curve (SUCRA)

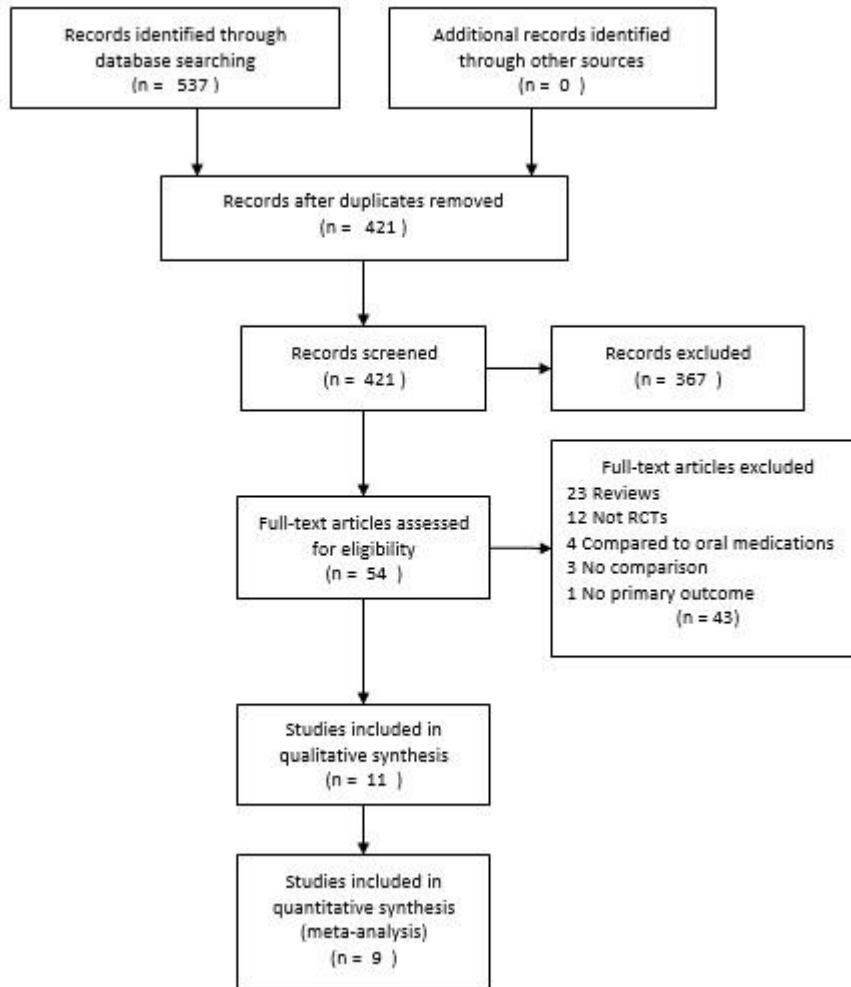
Treatment	SUCRA (%)	Rank
Gen	77.4	1
MP	67.5	2
Lat	57.4	3
Dex	52.8	4
Gan	28.6	5
Pla	16.3	6

Gen: Gentamicin, MP: Methylprednisolone, Lat: Latanoprost, Dex: Dexamethasone, Gan: Ganciclovir, Pla: Placebo

Table 4 Rank by SUCRA only including studies with follow-up time equal to or more than 24 months

Treatment	SUCRA (%)	Rank
Gen	68.4	1
MP	63.6	2
Dex	47.2	3
Pla	20.7	4

Gen: Gentamicin, MP: Methylprednisolone, Dex: Dexamethasone, Pla: Placebo



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Anaya(2005)	?	+	+	+	+	+	+
Bremer (2014)	+	+	+	+	-	+	-
Casani (2012)	?	-	-	-	+	+	+
Guyot (2008)	+	+	+	+	+	-	+
Masoumi (2017)	-	?	?	+	+	+	+
Patel (2016)	+	+	+	+	+	+	+
Postema (2008)	-	+	?	-	-	+	+
Rask-Andersen (2005)	?	?	+	+	+	+	+
Stokroos (2004)	?	+	+	+	+	+	+

