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Steroids for idiopathic sudden sensorineural hearing loss (Review)

Wei BPC, Stathopoulos D, O'Leary S

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[Intervention Review]

Steroids for idiopathic sudden sensorineural hearing loss

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ABSTRACT

Background

This is an update of a Cochrane review first published in *The Cochrane Library* in Issue 1, 2006 and previously updated in 2009.

Idiopathic sudden sensorineural hearing loss (ISSHL) is a clinical diagnosis characterised by a sudden deafness of cochlear or retrocochlear origin in the absence of a clear precipitating cause. Steroids are commonly prescribed to treat this condition. There is no consensus on their effectiveness.

Objectives

To determine whether steroids in the treatment of ISSHL a) improve hearing (primary) and b) reduce tinnitus (secondary).

To determine the incidence of significant side effects from the medication.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the most recent search was 22 April 2013.

Selection criteria

We identified all randomised controlled trials (with or without blinding) in which steroids were evaluated in comparison with either no treatment or a placebo. We considered trials including the use of steroids in combination with another treatment if the comparison control group also received the same other treatment. The two authors reviewed the full-text articles of all the retrieved trials of possible relevance and applied the inclusion criteria independently.

Data collection and analysis

We graded trials for risk of bias using the Cochrane approach. The data extraction was performed in a standardised manner by one author and rechecked by the other author. Where necessary we contacted investigators to obtain the missing information. Meta-analysis was neither possible nor considered appropriate because of the heterogeneity of the populations studied and the differences in steroid formulations, dosages and duration of treatment. We analysed and reported the quality of the results of each study individually. A narrative overview of the results is presented.

Main results

Only three trials, involving 267 participants, satisfied the inclusion criteria and all three studies were at high risk of bias. One trial showed a lack of effect of oral steroids in improving hearing compared with the placebo control group. The second trial showed a significant improvement of hearing in 61% of the patients receiving oral steroid and in only 32% of the patients from the control group (combination of placebo-treated group and untreated control group). The third trial also showed a lack of effect of oral steroids in improving hearing compared with the placebo control. However, this trial did not follow strict inclusion criteria for participant selection and analysis of data was limited by significant exclusion of participants from the final analysis and lack of participant compliance to the treatment protocol. No clear evidence was presented in two trials about any harmful side effects of the steroids. Only one study declared that no patients suffered from adverse effects of the steroid treatment.

Authors' conclusions

The value of steroids in the treatment of idiopathic sudden sensorineural hearing loss remains unclear since the evidence obtained from randomised controlled trials is contradictory in outcome, in part because the studies are based upon too small a number of patients.

PLAIN LANGUAGE SUMMARY

Steroids for the treatment of sudden hearing loss with unknown cause

A sudden onset of hearing loss due to disease of the hearing organs is a medical emergency and requires prompt recognition and treatment. In addition to the hearing impairment, patients may also suffer from symptoms of tinnitus (background ringing noise), a sensation of ear fullness and dizziness. In many instances medical specialists are able to find the cause and treat the hearing impairment. However, in a large proportion of patients, no known cause of the sudden hearing loss can be found. Steroids are commonly used to treat patients with sudden hearing loss of an unknown origin. The specific action of the steroids in the hearing apparatus is uncertain. It is possible that the steroid treatment improves hearing because of its ability to reduce inflammation and oedema (swelling) in the hearing organs. The review of the trials showed a lack of good-quality evidence for the effectiveness of steroids in the treatment of sudden hearing loss of an unknown origin. The quality of the trials was generally low and more research is needed.

BACKGROUND

This is an update of a Cochrane review first published in *The Cochrane Library* in Issue 1, 2006 and previously updated in 2009.

Description of the condition

Idiopathic sudden sensorineural hearing loss (ISSHL) is a clinical diagnosis, characterised by a sudden deafness of cochlear or retrocochlear origin, in the absence of a clear precipitating cause. Its incidence has been estimated at 8 to 15 per 100,000 persons per year (Hughes 1996; Stokroos 1996a).

The aetiology of idiopathic sudden sensorineural hearing loss remains obscure. Different theories attempt to explain this problem including disturbance of cochlear blood flow, viral infections, autoimmune disease and Reissner's membrane rupture (Cole 1988; Shikowitz 1991; Thurmond 1998). Theories presently favoured include a viral or vascular event within the cochlea giving rise to a sudden elevation in hearing thresholds and a degradation in speech discrimination. The natural history is variable, with some patients suffering from permanent hearing threshold changes, whilst others recover some degree of hearing following the insult (Shikowitz 1991).

Description of the intervention

Treatments for ISSHL have been aimed at recovery of hearing thresholds. The development of rational treatments for ISSHL has been hampered by uncertainty over the aetiology of the condition; treatments proposed have been based upon hypotheses of aetiology rather than firm evidence. Treatment modalities trialled include the use of individual or combination agents including vasodilators, diuretics, anticoagulants, plasma expanders, corticosteroids, contrast dye (Shikowitz 1991) and hyperbaric oxygen. Evaluation of treatments has been hampered by the low incidence of ISSHL, and the tendency for hearing to recover spontaneously (65% to 66%) (Mattox 1989). The latter has made the contribution of the treatment to hearing recovery difficult to evaluate.

How the intervention might work

21-amino glucocorticoid steroids, such as methylprednisolone, are commonly prescribed to treat this condition, but their usage is associated with potential side effects (Haberkamp 1999; Stokroos 1996b; Thurmond 1998). The specific action of steroids in the cochlea is uncertain but their use has been based on their ability to decrease inflammation and oedema. However, there are a wide range of side effects relating to short-term steroid use including glucose intolerance, hypertension, adrenal suppression, gastrointestinal bleeding and altered mental states. There are currently insufficient clinical data to indicate the prevalence of side effects from short, sharp courses of steroid usage. The duration of steroid usage for the treatment of ISSHL is very short (only about two weeks) compared with regimens used to treat chronic disease. The potential side effects from very short, sharp courses of steroids are therefore fewer than those from longer-term use.

Why it is important to do this review

We carried out a systematic review to examine the effectiveness of steroid usage in idiopathic sudden sensorineural hearing loss in order that the benefits of treatment could be weighed against the associated potential risks.

OBJECTIVES

1. To determine whether steroids in the treatment of ISSHL:
   a. improve hearing (primary);
   b. reduce tinnitus (secondary).
2. To determine the incidence of significant side effects from the medication.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients of any age with ISSHL and treated with steroids were included. These patients had to fit the entry criteria as below.

Idiopathic sudden sensorineural hearing loss (ISSHL) was defined as:

1. a history of a sudden decrease in hearing;
2. a sensorineural hearing loss demonstrable on a pure-tone audiogram at the time of entry into the trial (as it was anticipated that limited data would be available, a criterion for sensorineural hearing loss was not predefined);
3. no other neurological signs except the eighth cranial nerve defect;
4. commencement of treatment within 14 days of the onset of the hearing loss.

Exclusion criteria included:

- all other types of sensorineural hearing loss, or conductive forms of hearing impairment;
- a history of fluctuating sensorineural hearing loss.

Types of interventions

- Steroids versus placebo
- Steroids versus no treatment
- (Steroids + other treatment) versus (placebo + same other treatment)
- (Steroids + other treatment) versus (same other treatment)

Other trialled treatment modalities for ISSHL include vasodilators, antivirals, anticoagulants, hyperbaric oxygen, etc.

We planned to stratify the other treatment modalities with or without steroids according to their specific types, and also the gender and age of the patients, before comparison between the steroids and non-steroids groups. It has been established that connective tissue diseases and autoimmune diseases are more common in females than males, therefore hearing impairment due to undiagnosed or unknown immune diseases in the female population may be higher than the male population. In order to remove this potential confounder, it is important that the studied populations are stratified according to gender before comparing

the hearing improvement of the steroid-treated group to that of the placebo control.

Types of outcome measures

We assessed the following outcomes:

- an objective improvement in pure-tone thresholds, speech discrimination or both (as the data available for review were limited there was no predefined criterion for improvement, rather the hearing outcome was dichotomised (into improvement or no improvement) according to the criteria set in each study);
- relief of tinnitus;
- side effects (for example, gastrointestinal bleeding, mood alteration or psychosis, glucose intolerance or avascular necrosis of the head of the femur); and
- the morbidity and mortality of non-steroid treatments used in association with the steroids.

Outcomes were to be measured and assessed both within seven to 30 days (short-term) and one to 12 months (long-term) after treatment. As a meta-analysis was not appropriate in this review due to the insufficient quality of the data, we performed a qualitative systemic review.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 22 April 2013, following previous searches in 2009 and 2006.

Electronic searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2013, Issue 3); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; ISRCTN; ClinicalTrials.gov; ICTRP; Google Scholar and Google. In searches prior to 2013, we also searched BIOSIS Previews 1926 to 2012.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011)). Search strategies for the major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned reference lists of identified studies for further trials. We searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials. Abstracts from conference proceedings were sought via the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

Data collection and analysis

Selection of studies

One author scanned the initial search results to identify trials that loosely met the inclusion criteria. The first two authors then reviewed the full-text articles of the retrieved trials and applied the inclusion criteria independently. The authors were blind to the names of journal, study authors and the study results whilst applying the criteria for determining which studies to include in the review.

Any differences in opinion about which studies to include in the review were resolved with open discussion and referral to the review group Co-ordinating Editor.

Data extraction and management

Data from the studies were extracted by one author and rechecked by the other author. We performed data extraction using a standardised data form so as to allow an intention-to-treat analysis.

Study outcomes were measured using a variety of methods and we presented these in the most clinically relevant manner. Where the important data were missing from the study, one author wrote to the authors of the studies requesting further information.

For each trial we documented the following aspects:

- methods (including methods of allocation, blinding);
- participants (including ages, setting, inclusion/exclusion criteria, method of diagnosis);
- interventions (including dosage of steroids and duration; time interval between ISSHL and commencement of treatment; category of non-steroid treatment modalities used in combination with steroids); and
- outcomes (including definitions of hearing improvement and tinnitus, side effects of treatment, number of patients lost to follow-up, reasons for drop-out).

Assessment of risk of bias in included studies

In the original version of this review (2006) and the first update version (2009), we used a modification of the method used by Chalmers 1990 to assess study quality. At the second update of this review in 2013, we adopted the Cochrane 'Risk of bias' tool for the assessment of study quality. We undertook this assessment independently, with the following taken into consideration, as guided by the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

The 'Risk of bias' tool involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. The results of risk of bias are reported in 'Risk of bias' tables in the Characteristics of included studies.

Although we intended to use study quality for sensitivity analysis, we did not combine studies.

Data synthesis

We extracted data for an intention-to-treat analysis to include all randomised patients with ISSHL. As the data were not comparable or of sufficient quality we did not combine to give a summary measure of effect. In the current review we did not carry out sensitivity analysis due to the small numbers of the included trials. We calculated summary risk ratios for the reported outcomes.

If studies are located for future updates of this review, we will combine data to give a summary measure of effect. In the event that the data are combined, we will dichotomise the main outcome measure (recovery of hearing) into recovery or no recovery, so as to increase the sensitivity of the analysis since small patient numbers are anticipated. The following methods may be appropriate, depending upon the amount and quality of the future data. We will use approximate Chi^2 tests for homogeneity to assess comparability of included data ($P > 0.05$). We will construct a funnel plot to evaluate publication bias. We will analyse specific subgroups for the following factors: steroids and steroids with other interventions.

RESULTS

Description of studies

Results of the search

Of the 516 abstracts retrieved from our original search in 2004, 486 articles were excluded as these did not focus on idiopathic sudden sensorineural hearing loss, the treatment effect was not targeted primarily on steroids or the steroids were used as the control for the comparison of other treatments. After examining the remaining 30 studies in detail, only two studies were included in the review.

At the first update of this review in June 2009, our searches identified 84 potentially relevant references. However, following assessment we found that none met the inclusion criteria for the review. Thirteen were added to the excluded studies section (see below).

For the latest update of this review in 2013, our searches identified 187 potentially relevant references (after removal of duplicates). We discarded 114 references as these publications were not related to the effects of steroid on ISSHL. One additional study (Nosrati-Zarenoe 2012) was found to meet the inclusion criteria for the review. Four separate studies that described the outcome of corticosteroid treatment were reported in Nosrati-Zarenoe's thesis. Only one of the studies met the inclusion criteria for the review (Nosrati-Zarenoe 2012). The other three (Hultcrantz 2012; Nosrati-Zarenoe 2007; Nosrati-Zarenoe 2010) did not meet the criteria and were added to the excluded studies section (see below). Seventy studies in total were excluded from the review at the latest update.

Excluded studies were mainly non-randomised, not controlled and not double-blinded. Furthermore, in the majority of the excluded studies patients both in the control and the treatment group received systemic steroids, making it impossible to determine their true effect (see Excluded studies).

Included studies

Cinamon 2001, Nosrati-Zarenoe 2012 and Wilson 1980 were the three trials that satisfied the inclusion criteria. A summary of the methods, participants, interventions and outcomes of the included studies is shown in the table of Characteristics of included studies. Differences in the types of steroid formulation, dosage and the duration of treatment were observed between these three studies.

Design

Cinamon 2001 was a prospective, double-blind, placebo-controlled study used to evaluate the effectiveness of steroid or carbogen inhalation therapies. Randomisation was achieved on a rotational assignment; first patient to group one, second to group two, third to group three and so on.

Nosrati-Zarenoe 2012 was a prospective, double-blind, placebo-controlled, multicentre study to evaluate the efficacy of a corticosteroid (prednisolone) in the treatment of ISSHL. The authors mentioned that neither the person who administered the treatment nor the person evaluating the response to treatment knew which treatment a particular participant was receiving. However, the authors did not clarify the method of randomised allocation of participants to each treatment group.

Wilson 1980 was a double-blind, controlled trial to determine the effectiveness of oral steroids in the treatment of ISSHL. The quality of randomisation of patients into the different study groups was poorly defined in the study.

Sample sizes

Cinamon 2001 recruited a total of 41 patients with unilateral ISSHL. A total of 103 participants with ISSHL were enrolled in the Nosrati-Zarenoe 2012 study. Wilson 1980 included a total of 123 patients with unilateral ISSHL.

Setting

Cinamon 2001 was carried out in the Chaim Sheba Medical Center, Israel, with ethics committee approval. Nosrati-Zarenoe 2012 took place in 14 public otorhinolaryngological centres in Sweden. The study was approved by the regional ethics review board and Swedish Medical Products Agency. Wilson 1980 was conducted in two separate centres in the USA (Kaiser-Permanente (K-P) and Massachusetts Eye and Ear Infirmary (MEEI)) by two separate administrators (Byl and Wilson).

Participants

Patients in Cinamon 2001 were members of the general community who were referred to and hospitalised in the medical centre. The inclusion criteria included a history of sudden sensorineural hearing loss (SNHL) not exceeding two weeks duration, a 20 dB or more hearing loss in at least three frequencies compared to the healthy ear, no prior history of sensorineural hearing loss and otological pathological history or otological findings. The exclusion criteria were patients with a chronic otological history, prior sudden deafness, pathological otoscopic findings and medical conditions that made prescription of steroids unsafe. For example, patients with hypertension, diabetes or active peptic disease.

The participants' ages ranged between 12 and 71 years (average 36). There were 22 females and 19 males with 24 left and 17 right affected ears. The average duration from onset to initiation of

treatment was four days. The earliest time therapy began was on the day of hearing loss and the latest was nine days after onset.

The inclusion criteria in Nosrati-Zarenoe 2012 included a history of sudden onset hearing loss developing within 24 hours with unknown aetiology, no prior otological pathological history or otological findings, and a pure-tone average of 30 dB or more hearing loss in the affected ear of the three contiguous frequencies. The exclusion criteria were any medical condition rendering the use of corticosteroids unsafe. These included pregnancy, diabetes, chronic infections, peptic ulcer, uncompensated heart disease, recent surgery or psychiatric disease.

Participant ages ranged from 18 to 80 years (average 55). Ten participants were excluded from the analysis (four of them in the treatment group and six in the placebo group). The author did not clarify the reason for these exclusions. There were 53 males and 40 females with 47 left and 46 right affected ears. Enrolment and treatment was to start within seven days from the onset of hearing loss. Daily medication for concomitant disease was permitted except vascular, antiviral or corticosteroid treatment.

The inclusion criteria in the Wilson 1980 study included 30 dB of sensorineural hearing loss occurring in at least three contiguous frequencies in less than three days; patients were seen within 10 days of the onset of hearing loss; no prior treatment and no cause of the sudden hearing loss could be found. The exclusion criteria were patients for whom steroids would represent a hazard. These included pregnancy and poorly controlled diabetes.

The K-P study included 27 patients; 11 received steroids and 16 received placebo. The MEEI study included 92 patients; 22 received steroids, 18 were placebo controls and 52 were non-participant controls who elected not to participate in the double-blinded therapeutic trials. These non-participant controls were also analysed as an additional untreated control group. Four patients were excluded from the analysis as they insisted on receiving steroids as treatment and received steroids according to the protocol dosage schedule.

Interventions

Cinamon 2001 had four intervention groups:

Group 1: prednisolone tablets (1 mg/kg/day);
Group 2: placebo tablets which looked similar to the steroid tablets;
Group 3: carbogen (5% CO_2 + 95% oxygen) inhalation for 30 minutes, six times per day (every two hours during the day);
Group 4: room air inhalation for 30 minutes, six times per day (every two hours during the day).

Only the pharmacist and the study controller (who did not participate in the decision making) knew the real composition of the medications. The total duration of treatment was five days.

Prednisolone (in 10 mg capsules) or placebo was given as a single dose of 60 mg daily for three days in Nosrati-Zarenoe 2012. The dose was then reduced by 10 mg per day, with a total treatment period of eight days. If recovery was complete at day eight, participants were asked to stop the medication. A *complete recovery* was defined as a difference of less than 10 dB between the initial audiogram and the follow-up audiogram. In the absence of hearing improvement, the medication was continued at 10 mg daily to a total of 30 days.

In Wilson 1980 all patients were treated within 10 days of the hearing loss. However, the type, dosage and duration of the steroid treatment were different between the two study centres. In the K-P study, the steroid treatment group received a tapering oral dexamethasone dose over 10 days. In the MEEI study oral methylprednisolone with a different tapering dose was used over 12 days. The authors did not clarify the nature of the placebo and its dosage schedule.

Outcomes

Outcome measurement in Cinamon 2001 was based on objective audiometry. This was performed on admission, on day six and at follow-up (range 14 to 90 days, average 33 days). The authors evaluated and compared the average hearing level at six frequencies (250 to 8000 Hz), the pure-tone average of speech frequencies (500, 1000, 2000 Hz) and the high-tone average (4000, 8000 Hz). An 'improvement' was considered to be a minimum 15 dB change between the average hearing level evaluated at the different times mentioned. The patients who had vertigo at the onset of the disease were compared to the study population that did not suffer from vertigo. Four configurations of audiometric curves were defined for analysis of its effect on hearing recovery. These were up slope, down slope, 'U' shape and flat curve.

The outcome was measured with follow-up audiograms at day eight of treatment, one month and three months in Nosrati-Zarenoe 2012. If recovery was complete at day eight, the participants did not return for the one-month visit and were only asked to return for the three-month visit.

In Wilson 1980 the outcome was measured with follow-up audiograms at four weeks and three months after the onset of hearing loss. The hearing in the contralateral unaffected ear, measured at the four-week follow-up, was used as a standard for comparison of hearing improvement of the affected ear. A 'complete recovery' was defined as recovery of hearing to within 10 dB of the unaffected ear speech reception score or averaged pure-tone score (if loss was primarily in the high frequency range). A 'partial recovery' was defined as recovery of hearing to within 50% or more of the unaffected ear's speech reception score or averaged pure-tone score. 'No recovery' was defined as less than 50% recovery of hearing. For statistical analysis, complete and partial recovery groups were combined.

Excluded studies

Twenty-eight papers (Alexiou 1999; Arellano 1997; Asada 1998; Byl 1984; Chandrasekhar 2001; Dauman 1985; Echarri 2000; Edamatsu 1985; Gianoli 2001; Grandis 1993; Huang 1989; Kanzaki 1988; Kanzaki 2003; Kitajiri 2002; Kitamura 1996; Kopke 2001; Kubo 1988; Leong 1991; Mattox 1977; Minoda 2000; Moskowitz 1984; Nickisch 1987; Orchi 1998; Pyykkö 1997; Shiraishi 1991; Suzuki 2003; Wilkins 1987; Zadeh 2003) were excluded after review as they were non-randomised and non-controlled trials. The summary for each excluded studies is shown in the table of Characteristics of excluded studies.

Thirteen further studies were added to the Characteristics of excluded studies table at the update of this review in June 2009 (Aoki 2006; Chen 2003; Fujimura 2007; Fuse 2002; Gouveris 2005; Herr 2005; Kawamata 2007; Roebuck 2006; Shin 2007; Slattery 2005a; Slattery 2005b; Suzuki 2008; Xenellis 2006). Eleven were non-randomised studies.

Seventy further studies were added to the Characteristics of excluded studies table at the update of this review in 2013 (Ahn 2006; Ahn 2010; Ai 2009; Alimoglu 2011; Angeli 2012; Arslan 2011; Bae 2013; Barriat 2012; Battaglia 2008; Baysal 2013; Behnoud 2009; Bianchin 2010; Bittar 2009; Cekin 2009; Chan 2009; Chen 2010; Chen 2011; Choi 2011; Choung 2005; Clary 2011; Dallan 2010; Dallan 2011; Dispenza 2011; Filipo 2010; Filipo 2012; Fu 2011; Gouveris 2011; Han 2008; Han 2009; Hong 2009; Hultcrantz 2012; Hunchaisri 2010; Joong 2005; Jun 2012; Kara 2010; Kasapoglu 2009; Kim 2011a; Kim 2011b; Lee 2008; Lee 2011; Li 2010; Li 2011; Lim 2013; Liu 2011; Min 2011; Moon 2011; Mosges 2009; Nakagawa 2010; Nosrati-Zarenoe 2007; Nosrati-Zarenoe 2010; Ogawa 2002; Panda 2008; Park 2009; Park 2011; Peng 2008; Penido 2009; Plontke 2009; Rauch 2011; Sakata 2010; She 2010; Suoqiang 2012; Suzuki 2012; Tsai 2011; Wang 2012; Wu 2011; Yang 2010; Yang 2011; Zernotti 2009; Zhao 2009; Zhou 2011).

Risk of bias in included studies

Allocation

Randomisation

The number of patients in Cinamon 2001 was 41 and they were distributed into four different study groups. As the participant numbers were too few, the randomisation process was not adequate. Due to the low recruitment levels, there was (by chance) an uneven distribution of patients with known, and conceivably unknown, factors that could affect the treatment result. For example, the steroid study group had fewer patients with vertigo and tinnitus. Furthermore, four different shaped audiograms identified at the initial audiometry hearing assessment were unevenly distributed in the four study groups, with the carbogen treated group having the majority of the downward-sloping audiometric curves.

In Nosrati-Zarenoe 2012, 103 patients with ISSHL were randomised evenly to treatment with either prednisolone (51 participants) or placebo (52 participants). The randomisation appeared to be adequate as there was an even distribution of gender, age, audiogram types, onset and severity of hearing loss, and associated symptoms of tinnitus and vertigo (P value greater than 0.05).

There is evidence in Wilson 1980 that the randomisation was inadequate and that this resulted in a selection bias. This conclusion is supported by the uneven distribution of the age, symptom of vertigo, audiogram types and number of the participants between the different treatment groups and between the two centres. For example, 52% of the MEEI patients were younger than 40 years and 33% had vertigo, while in the K-P study only 28% were younger than 40 years and 81% had vertigo. Furthermore, there were 86 participants in the control group and only 33 patients in the steroid treatment group.

The author also erroneously assumed that the untreated control group and the placebo group were similar enough to be combined as one single control group for comparison. This significantly increased the control group population compared with the small number of participants in the steroid treatment group. This nullified the effects of randomisation and introduced confounders into data analysis.

Allocation concealment

In Cinamon 2001, the allocation was made on a rotation basis; first patient to group one, second to group two, third to group three and fourth to group four. This method of randomisation did not provide adequate concealment as the investigators would know which patient entered which group. To achieve a complete allocation concealment the participants should only find out which study group they were in after the allocation. In this study the investigators (and potentially the participants) would know whether they were in the steroid/placebo study groups or inhalation carbogen/placebo groups during the allocation process.

In Nosrati-Zarenoe 2012, the allocation concealment was not clearly defined. There was insufficient information to assess whether the randomisation provided adequate concealment of the treatments to both the investigators and the participants. In proper allocation concealment, participants and the investigators should not be able to alter the assignment or the decision of eligibility. After participants were assigned to the treatment groups, 10 participants (four from the prednisolone group and six from the placebo group) were removed from the study, as they did not fit the inclusion criteria. A participant was diagnosed with acoustic neuroma and hearing loss and was assigned to the prednisolone group. There were inconsistencies in the allocation of the participants and inclusion criteria for the study.

In Wilson 1980, allocation concealment was not mentioned and was assessed to be inadequate as 52 patients elected not to have treatment during the allocation process. Thus the patients and the investigators knew which group of patients were in the untreated control group. This raised different possibilities that could influence the outcome of the result. Would those patients who chose not to have treatment have a less severe disease? Were they taking other medications in private settings? Was there an early spontaneous recovery after the allocation and before initiation of the treatment? Furthermore, the authors declared that 14 patients with mid-frequency hearing loss had complete recovery (within 10 dB of all frequencies tested). The propensity for recovery in this group was recognised early in the study and these patients were not included in the double-blinded medication trials for fear that steroids would jeopardise their chance of recovery. Subsequently they were reallocated to the untreated control group.

Blinding

Blinding after allocation in Cinamon 2001 was adequate to reduce performance and detection biases. Both the steroid and placebo tablets looked the same and were marked as "Prednisone A" or "Prednisone B". Only the pharmacist and the study controller (who did not participate in the decision making) knew the real composition of the medications. However, there was no mention of independent blinded assessors in this study.

The authors of Nosrati-Zarenoe 2012 described the study as a triple-blind trial in which neither the participant, the person administering the treatment nor the person evaluating the response to treatment knew which treatment a particular participant was receiving.

Blinding after allocation was also unclear in Wilson 1980. Although the authors declared that the study was double-blind, they did not describe whether the patients or the administrators could separate the placebo tablets from the steroid tablets. The control group that

received no treatment was not blinded in this study as they knew they did not receive any tablets. There was no mention of the use of independent blinded assessors in this study. The study authors did not respond to our request for information relating to the degree of blinding.

Incomplete outcome data

There was no loss to follow-up or drop-out from Cinamon 2001 and intention-to-treat analysis was performed by the authors.

In Nosrati-Zarenoe 2012, the intention-to-treat analysis was not achieved as 30 patients were excluded from the analysis after they were assigned to the study groups. Ten of these participants did not fulfil the study's inclusion criteria and were excluded after allocation. The remaining 20 participants were excluded from the total analysis protocol as they did not take the medication as per the study design. The lack of compliance with the treatment protocol and the exclusion of the participants who did not comply could induce bias into the final analysis by reducing the power of the study. This would favour a lack of hearing improvement in the prednisolone-treated group.

In Wilson 1980, the intention-to-treat analysis was not achieved as four patients were excluded from the study and 14 patients were reallocated to the control group after the initial allocation.

Selective reporting

There was no selective reporting in Cinamon 2001. In Nosrati-Zarenoe 2012, the authors selectively removed 30 participants from final analysis and reporting. The authors did not explain the reasons for the lack of compliance with the study protocol of many participants. These patients' results were not reported and they were excluded from the final analysis. Furthermore, the authors failed to report and carry out the one-month audiometric examination which was stated in the study protocol. In Wilson 1980, the authors selectively reported subgroup analysis of only 74 patients and did not report the analysis of 34 patients with hearing loss of greater than 90 dB and 14 patients with mid-frequency loss.

Other potential sources of bias

Quality of outcome assessment

The outcome assessment in Cinamon 2001 was based on objective hearing audiometry assessment. The average hearing at six frequencies, pure-tone average of speech frequencies and the high-tone average of the affected ear were compared with the unaffected ear within each group. The degrees of hearing improvement were compared between the different study groups. The assumption made by the authors was that the pre-morbid hearing was the same in both the affected and the contralateral, unaffected ear. There was a potential for a measurement bias from this assumption. Pre-morbid hearing in the affected ear might be 10 dB worse than the other ear. Thus a measured improvement of 20 dB compared with the contralateral normal ear is different from the real improvement of a difference of 10 dB. As the criterion for improvement of hearing was defined as a minimum of 15 dB change between the average hearing levels, this could change the patients' study outcome from an improvement to no improvement.

In Nosrati-Zarenoe 2012, the outcome assessment was based on objective hearing audiometry assessment within 24 hours of hearing loss, eight days after treatment, one month and three months after the onset of ISSHL. The hearing loss was characterised by comparing the first audiogram taken after the onset of ISSHL to an audiogram taken not more than two years before the acute hearing loss. The assumption made by the authors was that the pre-morbid hearing 12 to 24 months ago was the same before the onset of the ISSHL, not better or worse. This assumption has the potential to create a measurement bias by either over or under estimating the degree of ISSHL at the time of recruitment, and the consequent analysis of the effects of the treatments (prednisolone and placebo) on hearing recovery. Furthermore, the authors did not carry out the complete outcome assessment protocol as seen by the absence of audiometric examination findings at one-month review.

If no previous audiogram was available, hearing was compared to the non-affected ear in its present state. Like the Cinamon 2001 and Wilson 1980 studies, the same assumption was made by Nosrati-Zarenoe et al. The hearing in the unaffected ear was assumed to be the same as the pre-morbid hearing of the affected ear. The potential for a measurement bias from this assumption is discussed in the methodological analysis of the Cinamon 2001 study.

The outcome assessment of Wilson 1980 was based on objective hearing audiometry assessment. The percentages of patients with defined hearing improvement were compared between different study groups. Like the Cinamon 2001 study, the same assumption was also made by Wilson et al. The hearing in the unaffected ear was assumed to be the same as the pre-morbid hearing in the affected ear. There was a potential for a measurement bias from this assumption. The reason for this is discussed in the methodological analysis of the Cinamon 2001 study. In the Wilson 1980 study, a "complete recovery" was defined as recovery of hearing to within 10 dB of the unaffected ear for either the speech perception score or averaged pure-tone score.

Furthermore, the definition of a "partial recovery" also has the potential to introduce bias. This was defined as a recovery of hearing within 50% or more of the pre-hearing loss speech reception score or averaged pure-tone score. A hearing improvement from 90 dB to 45 dB in a patient with pre-morbid hearing of 10 dB is not within the 50% of pre-hearing level. However, an improvement from 60 dB to 30 dB in a patient with pre-morbid hearing of 20 dB is within the 50% level. The former case would not be classified as a partial improvement and the latter would be considered as a partial improvement.

Quality of intervention

In Wilson 1980, there were problems with the study population. As the study was carried out in two different independent centres, there was a heterogeneity of the population between the two centres. Furthermore, the types of steroids, dosage and duration of the steroid treatment were different between the two centres. The relative potency of oral dexamethasone to prednisolone ranged from 10:1 to 12.5:1. The relative potency of methylprednisolone to prednisolone is 5:4. Thus, after conversion, the relative potency of the corticosteroids between the K-P and MEEI centres (K-P:MEEI) ranged from 592:380 to 740:380. Therefore the K-P study group received significantly greater effective doses of steroids than the MEEI group.

Effects of interventions

Three studies were included in the review, involving 267 participants. No conclusions can be drawn about the effectiveness,

or lack thereof, of steroids in the treatment of idiopathic sudden sensorineural hearing loss. The current studies were too poor in quality to provide convincing evidence supporting steroid use. In addition, there were too many confounding factors for the authors to draw any decisive conclusion. For instance, the populations for both studies were too small and the dosage, formulation and duration of steroid treatment varied. When interpreting the outcomes of the studies, it is important to be aware that the definition of hearing recovery is different between the Cinamon 2001, Nosrati-Zarenoe 2012 and Wilson 1980 studies (see Risk of bias in included studies and Description of studies).

Cinamon 2001

In the Cinamon 2001 study, an early post-treatment improvement of the average hearing level at six frequencies (250 to 800 Hz) was found in 60% of the steroid-treated patients and in 63% of the placebo-treated patients (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.48 to 1.85; Analysis 1.2). At follow-up, improvement rates were 80% and 81% respectively (RR 0.98, 95% CI 0.64 to 1.48; Analysis 2.2). According to the authors' report, the statistical analysis (by ANOVA) of the improvement did not indicate a significant difference between the groups after treatment ($P < 0.1$) or at follow-up ($P < 0.1$).

Improvement results for average speech frequencies (500, 1000, 2000 Hz) were found in 60% of the steroid-treated population and 54% of the placebo-treated population (RR 1.10, 95% CI 0.52 to 2.30; Analysis 1.1). At follow-up, improvement rates were found to be 70% and 72% respectively (RR 0.96, 95% CI 0.56 to 1.66; Analysis 2.1). The Cinamon 2001 study declared in their analysis that there were no statistical differences between the groups with $P < 0.2$ at immediate post-treatment and with $P < 0.1$ at the follow-up assessment.

An improvement in high-tone hearing level average (4000, 8000 Hz) was found in 40% of the steroid group and 45% of the placebo group immediately after treatment (RR 0.88, 95% CI 0.32 to 2.39; Analysis 1.3). At follow-up, this was 60% and 64% respectively (RR 1.10, 95% CI 0.52 to 2.30; Analysis 2.3). The authors reported that there were no statistically significant differences between the groups, with $P < 0.1$ at immediate post-treatment and with $P < 0.1$ at follow-up.

Secondary outcomes including improvement of symptoms of tinnitus and vertigo were not measured in this study.

Furthermore, the authors carried out subgroup analysis of the effects of vertigo and the shapes of the audiometric curve in hearing recovery. They found no association between hearing improvement with the above variables. This is perhaps not surprising given the relatively small numbers of patients in each group, which led to an uneven distribution of patients with each audiogram configuration.

Finally, there was no documentation of the side effect profile from the steroid group. The study authors did not respond to the authors' request for such information.

Nosrati-Zarenoe 2012

In the Nosrati-Zarenoe 2012 study, the mean improvement of hearing in dB HL at day eight after the treatment was 25.5 dB in the prednisolone group and 26.4 dB in the placebo. Three months after the initial diagnosis of idiopathic sudden sensorineural hearing loss (ISSHL), the prednisolone-treated group achieved a mean of 39 dB hearing improvement compared to 35.1 dB of hearing improvement in the placebo-treated group. The authors reported no significant difference in hearing recovery between the prednisolone and the placebo group either at day eight or three months ($P > 0.05$).

There were several inconsistencies in the data analysis that could lead to further error. After excluding 10 participants from the study, 93 participants were analysed by modified intention-to-treat (ITT): 47 received prednisolone and 46 received placebo. However, 20 of the 93 participants did not take the drugs according to protocol and four participants missed the final three-month audiogram. The inclusion of these 24 participants in the final analysis could affect the outcome measures. The exclusion of these participants would reduce the power of the study and could lead to a biased result favouring no benefit with prednisolone treatment. The authors did not give a reason for the non-compliance with treatment protocol in the 20 participants. Could this be as a result of side effects? Alternatively, the participants may have decided to stop the medication when they noticed no change in hearing. In eight of 93 patients, hearing loss was evaluated by comparing an audiogram taken within two years prior to the ISSHL. The potential error from including this group of participants in the final analysis is discussed in the 'Quality of outcome assessment' section (Risk of bias in included studies). The authors described the analysis of the 73 participants who took the medication according to the protocol as "total per protocol" in the methods section of the publication. However, the result for these data was not provided. The methods section of the study also described audiometric assessment of the participants' hearing at one month after the onset of ISSHL. However, as these data were unavailable the investigators either did not carry out this protocol or selected not to report the data. The presentation of the data suggests another potential reporting error. The authors described the analysis of data including 93 participants. However, it was unclear if the authors had included or excluded the four participants with missing audiograms in the final analysis.

There is concern about the inclusion criteria for this study. There is evidence to suggest that the inclusion criteria were not strictly followed by the investigators. This is supported by the exclusion of 10 participants from the study after randomisation. Furthermore, the study also included one patient with non-idiopathic SSHL. This patient was diagnosed with acoustic neuroma. A selection bias could occur due to the inconsistent application of the inclusion criteria to the participants in the study. In the subgroup analysis, vertigo was the only negative prognostic factor for hearing recovery for both the prednisolone and placebo-treated group at the three-month follow-up ($P < 0.007$). Secondary outcomes, including improvement of the symptoms of tinnitus and vertigo, were not measured in this study. Finally, there was no documentation of the side effect profile from the prednisolone group.

Wilson 1980

In the Wilson 1980 study, the total percentage of patients with hearing improvement in the steroid group was 61% and in the placebo group was 32% (RR 1.30, 95% CI 0.91 to 1.86). However, this is the combination of results from two different centres with a different steroid dosage and different demographic patient groups. The authors adopted the pooling participants approach by simply adding up numbers of participants across the two centres.

However, due to the heterogeneity between the two centres, a weighted averages analysis approach was used to calculate the new RR, which was 1.40 (95% CI 0.99 to 1.97; Analysis 3.1).

When reported separately, the percentage of patients with hearing recovery in the MEEI trial was found to be 73% of the steroid group and 50% of the control group (RR 1.45, 95% CI 1.03 to 2.06; Analysis 3.1). In the K-P trial, 36% of the steroid group population and 31% of the placebo population were found to have hearing improvement (RR 1.16, 95% CI 0.40 to 3.38; Analysis 3.1).

The study authors then excluded the 34 patients with hearing loss of greater than 90 dB and 14 patients with mid-frequency loss to perform a subgroup analysis of the remaining 74 patients. When adding up the reported numbers above, a total of 122 patients is obtained and this is one patient short of the total number of participants reported in the study. These 74 patients were declared to be in the steroid-effective zone. They had hearing loss at 4 kHz greater than or equal to losses at 8 kHz or losses at 8 kHz greater than those at 4 kHz. In the MEEI trial, the percentage of patients recovered in the steroid group was 91% and 47% in the control group (RR 1.95, 95% CI 1.35 to 2.80; Analysis 4.1). In the K-P trial, 57% of the steroid group recovered and only 36% of the control group had hearing recovery (RR 1.57, 95% CI 0.57 to 4.32; Analysis 4.1). When the two groups were combined the overall recovery in the steroid group was 78% and in the placebo group 38% (RR 1.74, 95% CI 1.19 to 2.55). In the reporting of Wilson 1980 this was significant, with $P < 0.025$. With analysis by weighted averages the RR was calculated to be 1.84, 95% CI 1.27 to 2.68 (Analysis 4.1).

Once again care must be taken in interpreting conclusions, as there were selective reporting and analysis biases. First, there were only 18 patients in the steroid group and 56 patients in the control group. Furthermore, there were 20 patients with hearing loss at 4 kHz greater than or equal to losses at 8 kHz and 54 patients with losses at 8 kHz greater than those at 4 kHz. These two patient groups were combined as one group for analysis. The authors came to this decision based on the fact that there were no differences in these two audiogram types with regard to clinic (K-P versus MEEI), age, vertigo, treatment or recovery.

Secondary outcomes including improvement of symptoms of tinnitus and vertigo were not measured in this study.

Finally, all patients were able to tolerate steroids at the dosage prescribed without adverse side effects. There were no patients with worsening of hearing from steroid use.

DISCUSSION

The effectiveness of steroids in the treatment of idiopathic sudden sensorineural hearing loss (ISSHL) remains unproven.

We used a sensitive search strategy in order to identify as many studies of the treatment of ISSHL as possible and to avoid the potential for selection bias. We then applied strict inclusion criteria to retain only studies that were less likely to be biased. It became clear while undertaking this review that there were only three randomised controlled trials addressing the effectiveness and the safety profile of steroids in the treatment of ISSHL compared to a placebo control. The included studies were of poor quality and contained relatively small numbers of participants.

It was also clear that the degree of heterogeneity was too great between the studies to allow any aggregation of the results to draw conclusions. These included differences in the definition of hearing improvement, differences in the formulations, duration and dosage of the steroid intervention, variations in the participants' geographic background, differences in the means of assessing the outcomes and variations in the methodological quality of the studies.

Furthermore, the natural history of ISSHL is highly variable, probably because its pathogenesis is multifactorial. Spontaneous improvement frequently occurs early after the onset of the hearing loss, therefore the prognosis is worse the longer symptoms persist (Eisenman 2000; Gulya 1996). Therefore, prospective randomised controlled trials might be biased and prone to interpretive error, because not all patients can be seen at the same stage of the disease. Further bias could also result from a self selection process, whereby those who recover quickly do not seek medical care. The time from onset of the hearing loss to the onset of treatment varied from one to 10 days in the participants of both the Cinamon 2001 and Wilson 1980 studies. It is also difficult to determine the true effects of this on the outcome of the studies. In the Nosrati-Zarenoe 2012 study, one inclusion criterion was hearing loss within 24 hours, however many participants did not have a recent audiogram to compare with the audiogram at presentation of symptoms to confirm objectively that the hearing loss was within 24 hours.

The patient group under investigation might have been too small to achieve statistical significance. All the reviewed studies suffered from this limitation because of the low incidence of the condition, especially when exclusion criteria were strictly applied. Assuming that the observed or placebo patients had a recovery rate of 60% and those treated with steroids had a recovery rate of 70%, then the study would require randomisation of more than 1000 patients to have 90% power to detect this difference.

Lack of compliance with the treatment protocol (Nosrati-Zarenoe 2012) could also potentially result in bias toward a lack of effect of steroid in the treatment group compared to the placebo group.

The potential for bias was great in the Cinamon 2001 and Wilson 1980 studies because of the lack of proper allocation concealment in assembling the comparison groups. When assessing the eligibility of potential participants for a trial, those recruiting participants and participants themselves should remain unaware of the next assignment in the sequence until after the decision about eligibility has been made. After assignment has been revealed, they should not be able to alter the assignment or the decision about eligibility. In Wilson 1980, pre-allocation exclusion and reallocation occurred for 18 patients. In Nosrati-Zarenoe 2012, post-allocation exclusion occurred for 10 participants. Furthermore, the reporting of missing data in the analysis section of both studies was inadequate and inconsistent.

In Wilson 1980 and Cinamon 2001, subgroup analysis was performed for the four different audiometry configurations. It is important to remember that a difference in hearing recovery between the subgroups was based on an observational comparison, and might exist due to confounding by other factors. The conclusions that were drawn from this analysis were based on subdivision of the study and indirect comparison. A separate randomised controlled trial would be required to study the effects

of the patients' audiometric configuration on the treatment of ISSHL.

Finally, the studies Byl 1984 and Mattox 1977 published data on the rate of spontaneous recovery of patients with ISSHL. These data have been quoted and compared with the recovery rate of the steroid-treated patients in a number of the excluded studies listed in this review. Great caution should be taken in interpreting the conclusions of these excluded studies because in effect they were comparing people in the treatment group of one trial with people in the control group of another trial. There would be a difference in the characteristics of the study populations and in the way that the studies were carried out.

Since the original publication of this review in 2006, the trend has been to administer steroid via intratympanic routes. Assessment of the efficacy of intratympanic versus oral steroid administration on hearing recovery in patients with ISSHL is not the aim of this review. We focused on the effects of steroids (regardless of the routes of administration) on hearing recovery in participants with ISSHL compared to placebo. All current published literature on intratympanic steroid treatment has compared the efficacy of intratympanic versus oral administration. A Cochrane review on this topic is being undertaken (Plontke 2009a).

AUTHORS' CONCLUSIONS

Implications for practice

There is no good evidence to suggest the effectiveness or the lack of effectiveness of steroids in the treatment of idiopathic sudden sensorineural hearing loss (ISSHL). Furthermore, the incidence of side effects and the cost of steroid treatment in ISSHL still remain to be determined.

Implications for research

It is important that all future randomised controlled studies focus on the need to generate a comparison control group which is identical in every respect to the steroid treatment group. This is the only way to determine the real effects of the steroids. Randomisation is the only means of allocation that controls for unknown and unmeasured confounders as well as those that are known and measured. The groups would be more comparable if a larger study population was randomised. This would mean that we could be more certain about concluding that differences in outcome are due to the treatment.

However, due to the low incidence of ISSHL, it is difficult to produce comparable groups through randomisation when the study population is small. Thus stratification of key characteristics (e.g. age of patient, the time elapsed since the onset of hearing loss, types of audiometry configuration and vertigo), that were known to have possible effects on the outcome of hearing recovery, should be carried out before the process of randomisation. This would reduce the effects of uneven randomisation by chance.

Due to the low incidence of ISSHL, a multicentre clinical trial might be the solution to the lack of cases, despite the difficulty of providing identical levels of care to every patient presenting with this condition.

Finally, there is no uniform definition of what should be considered partial or complete hearing recovery and this will affect the outcome of individual studies. The interpretation of the results of current clinical trials is complicated by arbitrarily defined hearing improvement and a lack of quality assessment of its clinical significance. Further research and study in this area is also needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cinamon 2001

Methods	Randomised, double-blinded
Participants	Setting: general community patients suffering from unilateral ISSHL who were referred to Chaim Sheba Medical Center Country: Israel Total number: 41 Mean age: 36 Male to female ratio: 19/22 Tinnitus (no. of patients): 23 Vertigo (no. patients): 13 Duration of treatment: 5 days
Interventions	Group 1: prednisone tablet 1 mg/kg once a day Group 2: placebo tablets (similar to prednisolone tablets) Group 3: carbogen (5% CO2 + 95% oxygen) inhalation for 30 minutes, 6 times per day Group 4: room air inhalation for 30 minutes, 6 times per day
Outcomes	Outcome measures: objective audiometry performed on admission, on day 6 and at follow-up (range 14 to 90 days, average 33 days). The authors evaluated and compared the average hearing level at 6 frequencies (250 to 8000 Hz), the pure-tone average of speech frequencies (500, 1000, 2000 Hz) and the high-tone average (4000, 8000 Hz). An "improvement" was considered to be a minimum 15 dB change between the average hearing level evaluated at the different times mentioned.
Notes	Quality score: C
Risk of bias	

Bias	Authors' judgement	Support for judgement

Cinamon 2001 *(Continued)*

Random sequence generation (selection bias)	High risk	The randomisation was made on a rotation basis. This method of randomisation did not provide adequate concealment as the investigators would know which patient entered which group.
Allocation concealment (selection bias)	High risk	Inadequate. Based on sequential allocation of the participants to each treatment group. The investigators would know which patient entered which group.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the steroid and placebo tablets looked the same and were marked as "Prednisone A" or "Prednisone B". Only the pharmacist and the study controller (who did not participate in the decision making) knew the real composition of the medications.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up or drop-out from the study and intention-to-treat analysis was performed by the authors
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Low risk	

Nosrati-Zarenoe 2012

Methods	Randomised, triple-blind study
Participants	Setting: 14 public otorhinolaryngological centres in Sweden Total number: 103 (10 participants were excluded after random allocation to either control or prednisolone group) Mean age: 55 Male to female ratio: 53:40 Tinnitus (number of patients): 68 Vertigo (number of patients): 25 Duration of treatment: all participants were asked to complete 8 days of the medication. If the hearing recovery was not complete, the participants would take medication to a total of 30 days.
Interventions	Prednisolone versus placebo Prednisolone as 10 mg capsules, or placebo was given as a single dose of 60 mg daily for 3 days; the dose was then reduced by 10 mg per day, with a total treatment period of 8 days. If recovery was complete (complete recovery = difference between the initial audiogram and audiogram at the follow-up < 10 dB) treatment stopped, otherwise medication was continued at 10 mg daily to a total of 30 days.
Outcomes	The outcome assessment was based on objective hearing audiometry taken within 24 hours of hearing loss, 8 days after treatment, 1 month and 3 months after the onset of ISSHL. However, 1-month audiometric assessment was not performed and subsequently not reported in the result section. A complete recovery was defined as the difference between initial audiogram and audiogram at the follow-up < 10 dB. Partial recovery was defined as the difference ≥ 10 dB and the improvement ≥ 10 dB.
Notes	Quality score: C

Nosrati-Zarenoe 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants appeared to be equally distributed between the prednisolone and placebo groups
Allocation concealment (selection bias)	Unclear risk	There was no clear mention of allocation concealment of the study. After the participants were assigned to the treatment groups, 10 participants were excluded as they did not fit the study's inclusion criteria.
Blinding (performance bias and detection bias) All outcomes	Low risk	Neither the participant, the person administrating the treatment nor the person evaluating the response to treatment knew which treatment a particular participant was receiving
Incomplete outcome data (attrition bias) All outcomes	High risk	Final audiometric examinations were missing in 4 participants; 20 participants did not complete the treatment protocol
Selective reporting (reporting bias)	High risk	Too many participants were excluded from the study after randomisation. Many participants did not complete the study protocol. 1-month audiometric examination was either not carried out or not reported.
Other bias	Unclear risk	The trial was not carried out in strict compliance with the proposed methodology of the initial trial design

Wilson 1980

Methods	Double-blinded It is unclear whether randomisation took place in this study and if so the methodological process has not been described
Participants	Setting: 2 different centres, conducted by 2 different investigators (Kaiser-Permanente (K-P), Oakland and Massachusetts Eye and Ear Infirmary (MEEI), Boston) Country: USA Total number: 123 (however only 119 were included in the analysis and 4 were excluded after the study (K-P: 27 MEEI: 92)) Mean age: not known Male to female ratio: not mentioned Tinnitus (no. of patients): not mentioned Vertigo: K-P 61% and MEEI 33% Duration of treatment: K-P 10 days; MEEI 12 days
Interventions	K-P Treatment group: oral methylprednisolone 12 days Control group: placebo MEEI Treatment group: oral dexamethasone 10 days Control group 1: placebo Control group 2: no treatment
Outcomes	Outcome measures: objective audiometry performed on admission, at 4 weeks and 3 months after the onset of hearing loss. A "complete recovery" was defined as recovery of hearing to within 10 dB of the unaffected ear speech reception score or averaged pure-tone score (if loss was primarily in the high frequency range). A "partial recovery" was defined as recovery of hearing to within 50% or more of the un-

Wilson 1980 *(Continued)*

	affected ear's speech reception score or averaged pure-tone score. A "no recovery" was defined as less than 50% recovery of hearing.
Notes	Quality score: C

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	There is evidence that the randomisation was inadequate and that this resulted in a selection bias. This is supported by the uneven distribution of the age, symptom of vertigo, audiogram types and number of the participants between the different treatment groups and between the 2 centres.
Allocation concealment (selection bias)	High risk	Allocation concealment was not mentioned and was assessed to be inadequate as 52 patients elected not to have treatment during the allocation process
Blinding (performance bias and detection bias) All outcomes	High risk	The control group that received no treatment was not blinded in this study as they knew they did not receive any tablets. There was no mention of the use of independent blinded assessors in this study. The study authors did not respond to our request for information relating to the degree of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	The intention-to-treat analysis was not achieved as 4 patients were excluded from the study and 14 patients were reallocated to the control group after the initial allocation
Selective reporting (reporting bias)	High risk	The study authors then excluded the 34 patients with hearing loss of greater than 90 dB and 14 patients with mid-frequency loss to perform a subgroup analysis of the remaining 74 patients
Other bias	High risk	There were problems with the study population. As the study was carried out in 2 different independent centres, there was heterogeneity of the population between the 2 centres. Furthermore, the types of steroids, dosage and duration of the steroid treatment were different between the 2 centres.

ISSHL: idiopathic sudden sensorineural hearing loss
K-P: Kaiser-Permanente
MEEI: Massachusetts Eye and Ear Infirmary

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahn 2006	ALLOCATION Randomised, placebo-controlled but not double-blinded PARTICIPANTS 270 patients with SSHL INTERVENTION Patients were assigned to lipo-prostaglandin infusion over 5 days or saline (placebo group); all patients studied were treated with 48 mg methylprednisolone for 5 days Note: impossible to determine the true effects of steroid when both groups received steroid
Ahn 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled

Study	Reason for exclusion
Ai 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Alexiou 1999	ALLOCATION Not randomised, not double-blinded
Alimoglu 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Angeli 2012	ALLOCATION Not randomised, double-blinded or placebo-controlled
Aoki 2006	ALLOCATION Not randomised, double-blinded or placebo-controlled
Arellano 1997	ALLOCATION Not randomised, double-blinded or placebo-controlled
Arslan 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Asada 1998	ALLOCATION Not randomised, double-blinded or placebo-controlled
Bae 2013	ALLOCATION Not randomised, double-blinded or placebo-controlled
Barriat 2012	ALLOCATION Not randomised, double-blinded or placebo-controlled
Battaglia 2008	ALLOCATION Randomised, double-blinded, placebo-controlled, multicentre study PARTICIPANTS 51 patients with ISSHL INTERVENTION Intratympanic dexamethasone with placebo taper, high-dose prednisone taper with placebo intratympanic injections, intratympanic dexamethasone with high-dose prednisone taper Note: impossible to determine the true effects of steroid when there was no double placebo control (placebo intratympanic injections with placebo taper). This study compared the hearing recovery rate between different routes of steroid administration.
Baysal 2013	ALLOCATION Not randomised, double-blinded or placebo-controlled
Behnoud 2009	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 71 patients with SSHL INTERVENTION Steroid and hydration therapy with and without phlebotomy Note: impossible to determine the true effects of steroid when there was no placebo control
Bianchin 2010	ALLOCATION

Study	Reason for exclusion
	Randomised; not double-blinded or placebo-controlled PARTICIPANTS 132 patients with SSHL and high plasmatic levels of low-density lipoprotein cholesterol and/or fibrinogen INTERVENTION A standard treatment (glycerol and dexamethasone) with and without a single selective plasmapheresis Note: impossible to determine the true effects of steroid when there was no placebo control. Furthermore this study focused on a subgroup of patients who had high serum cholesterol and fibrinogen.
Bittar 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Byl 1984	ALLOCATION Not randomised, double-blinded or placebo-controlled
Cekin 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Chan 2009	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 19 patients with SSHL INTERVENTION Oral steroid versus intratympanic steroid Note: impossible to determine the true effects of steroid when there was no placebo control
Chandrasekhar 2001	ALLOCATION Not randomised, double-blinded or placebo-controlled
Chen 2003	ALLOCATION Not randomised, double-blinded or placebo-controlled
Chen 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Chen 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Choi 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Choung 2005	ALLOCATION Not randomised, double-blinded or placebo-controlled
Clary 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Dallan 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled

Study	Reason for exclusion
Dallan 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Dauman 1985	ALLOCATION Not randomised, double-blinded or placebo-controlled
Dispenza 2011	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 46 patients with SSHL INTERVENTION Oral versus intratympanic steroid treatment Note: impossible to determine the true effects of steroid when there was no placebo control
Echarri 2000	ALLOCATION Not randomised, double-blinded or placebo-controlled
Edamatsu 1985	ALLOCATION Not randomised, not double-blinded
Filipo 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Filipo 2012	ALLOCATION Not randomised, double-blinded or placebo-controlled
Fu 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Fujimura 2007	ALLOCATION Not randomised, double-blinded or placebo-controlled
Fuse 2002	ALLOCATION Not randomised, double-blinded or placebo-controlled
Gianoli 2001	ALLOCATION Not randomised, double-blinded or placebo-controlled
Gouveris 2005	ALLOCATION Not randomised, double-blinded or placebo-controlled
Gouveris 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Grandis 1993	ALLOCATION Not randomised, double-blinded or placebo-controlled
Han 2008	ALLOCATION Not randomised, double-blinded or placebo-controlled
Han 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Herr 2005	ALLOCATION

Study	Reason for exclusion
	Not randomised, double-blinded or placebo-controlled
Hong 2009	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 63 patients with ISSHL INTERVENTION Oral prednisolone versus intratympanic dexamethasone Note: impossible to determine the true effects of steroid when there was no placebo control
Huang 1989	ALLOCATION Not randomised, not double-blinded
Hultcrantz 2012	ALLOCATION Meta-analysis of data from a randomised controlled trial and a Swedish national database for ISSHL
Hunchaisri 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Joong 2005	ALLOCATION Not randomised, double-blinded or placebo-controlled
Jun 2012	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kanzaki 1988	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kanzaki 2003	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kara 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kasapoglu 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kawamata 2007	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kim 2011a	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kim 2011b	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kitajiri 2002	ALLOCATION Not randomised, not double-blinded
Kitamura 1996	ALLOCATION Not randomised, double-blinded or placebo-controlled
Kopke 2001	ALLOCATION

Study	Reason for exclusion
	Not randomised, double-blinded or placebo-controlled
Kubo 1988	ALLOCATION Randomised, no placebo control, paired double-blinded PARTICIPANTS 169 people with unilateral ISSHL from 5 medical schools and their affiliated hospitals in Japan INTERVENTION Combined intravenous and oral betamethasone versus intravenous batroxobin with oral placebo tablet Note: impossible to determine the true effects of steroid when there was no control
Lee 2008	ALLOCATION Not randomised, double-blinded or placebo-controlled
Lee 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Leong 1991	ALLOCATION Retrospective, not randomised, double-blinded or placebo-controlled
Li 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Li 2011	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 65 patients with SSHL INTERVENTION After the patients did not respond to intravenous treatment with prednisolone, they were randomised into 3 groups: treatment with intratympanic methylprednisolone, treatment with methylprednisolone in ear drops and a blank control Note: impossible to determine the true effects of steroid when there was no placebo control
Lim 2013	ALLOCATION Randomised but not double-blinded or placebo-controlled
Liu 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Mattox 1977	ALLOCATION Not randomised or placebo-controlled
Min 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Minoda 2000	ALLOCATION Not randomised, double-blinded or placebo-controlled
Moon 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Mosges 2009	ALLOCATION Randomised; not double-blinded or placebo-controlled

Study	Reason for exclusion
	PARTICIPANTS 240 patients with SSHL INTERVENTION Rheopheresis treatment versus intravenous corticosteroids versus intravenous haemodilution Note: impossible to determine the true effects of steroid when there was no placebo control
Moskowitz 1984	ALLOCATION Not randomised, not double-blinded
Nakagawa 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Nickisch 1987	ALLOCATION Not randomised, double-blinded or placebo-controlled
Nosrati-Zarenoe 2007	ALLOCATION Not randomised, double-blinded or placebo-controlled
Nosrati-Zarenoe 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Ogawa 2002	ALLOCATION Randomised, double-blinded and placebo-controlled PARTICIPANTS 57 patients with ISSHL INTERVENTION Intravenous prostaglandin E1 and hydrocortisone versus intravenous placebo and hydrocortisone Note: impossible to determine the true effects of steroid when there was no placebo control and both intervention groups received systemic steroid. This study was designed to examine the effect of prostaglandin E1 on ISSHL.
Orchi 1998	ALLOCATION Not randomised, double-blinded or placebo-controlled
Panda 2008	ALLOCATION Not randomised, double-blinded or placebo-controlled
Park 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Park 2011	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 88 patients with SSHL INTERVENTION 1) Intratympanic dexamethasone was given simultaneously initially with systemic steroid 2) Intratympanic dexamethasone was given 7 days after systemic steroid treatment Note: impossible to determine the true effects of steroid when there was no placebo control
Peng 2008	ALLOCATION Randomised; not double-blinded or placebo-controlled

Study	Reason for exclusion
	PARTICIPANTS 84 patients with ISSHL INTERVENTION Oral dexamethasone plus conventional methods (n = 21), intravenous dexamethasone plus conventional methods (n = 21), and intratympanic dexamethasone plus conventional methods (n = 21), intratympanic dexamethasone injection by the way of pharyngotympanic tube combined with conventional methods (n = 21) Note: impossible to determine the true effects of steroid when there was no placebo control. Furthermore, the total amount of steroid received was different by each route of administration.
Penido 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Plontke 2009	ALLOCATION Randomised, double-blinded and placebo-controlled PARTICIPANTS 23 patients with ISSHL INTERVENTION Systemic high-dose glucocorticoid therapy followed by either dexamethasone or placebo (saline 0.9%) continuously applied for 14 days into the round window niche via a temporarily implanted catheter Note: impossible to determine the true effects of steroid when there was no placebo control (participants without any systemic and local steroid treatment)
Pyykkö 1997	ALLOCATION Not randomised, double-blinded or placebo-controlled
Rauch 2011	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 250 patients with ISSHL INTERVENTION Intravenous methylprednisolone versus oral prednisone Note: impossible to determine the true effects of steroid when there was no placebo control
Roebuck 2006	ALLOCATION Not randomised, double-blinded or placebo-controlled
Sakata 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
She 2010	ALLOCATION Not randomised, double-blinded or placebo-controlled
Shin 2007	ALLOCATION Randomised but not double-blinded or placebo-controlled PARTICIPANTS 44 participants with ISSHL who did not respond to 1 cycle of oral prednisolone with intravenous acyclovir and volume expander (intravenous pentastarch) INTERVENTION

Study	Reason for exclusion
	Second cycle of oral prednisolone therapy versus no treatment
Shiraishi 1991	ALLOCATION Paired double-blinded, unclear randomisation and no placebo control PARTICIPANTS 168 people with unilateral ISSHL from 5 multi-institutions in Japan INTERVENTION Combined intravenous and oral betamethasone versus intravenous batroxobin with oral placebo tablet Note: impossible to determine the true effects of steroid when there was no control
Slattery 2005a	ALLOCATION Not randomised, double-blinded or placebo-controlled
Slattery 2005b	ALLOCATION Not randomised, double-blinded or placebo-controlled
Suoqiang 2012	ALLOCATION Not randomised, double-blinded or placebo-controlled
Suzuki 2003	ALLOCATION Not randomised, double-blinded or placebo-controlled
Suzuki 2008	ALLOCATION Not randomised, double-blinded or placebo-controlled
Suzuki 2012	ALLOCATION Not randomised, double-blinded or placebo-controlled
Tsai 2011	ALLOCATION Not randomised, double-blinded or placebo-controlled
Wang 2012	ALLOCATION Not randomised, double-blinded or placebo-controlled
Wilkins 1987	ALLOCATION Not randomised, double-blinded or placebo-controlled
Wu 2011	ALLOCATION Randomised, double-blinded and placebo-controlled PARTICIPANTS 60 patients with ISSHL who did not respond to an initial round of steroid treatment INTERVENTION After failure of systemic steroid treatment, patients were given either intratympanic steroid or saline Note: impossible to determine the true effects of steroid when there was no double placebo control of patients who received neither systemic nor intratympanic steroid
Xenellis 2006	ALLOCATION Not randomised, double-blinded or placebo-controlled
Yang 2010	ALLOCATION

Study	Reason for exclusion
	Not randomised, double-blinded or placebo-controlled
Yang 2011	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 66 patients with SSHL INTERVENTION Oral corticosteroid treatment with and without oral zinc gluconate Note: impossible to determine the true effects of steroid when there was no placebo control
Zadeh 2003	ALLOCATION Not randomised, double-blinded or placebo-controlled
Zernotti 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Zhao 2009	ALLOCATION Not randomised, double-blinded or placebo-controlled
Zhou 2011	ALLOCATION Randomised; not double-blinded or placebo-controlled PARTICIPANTS 76 patients with ISSHL INTERVENTION Intratympanic steroid versus no treatment in patients who did not respond to the initial systemic steroid therapy Note: impossible to determine the true effects of steroid when there was no placebo control

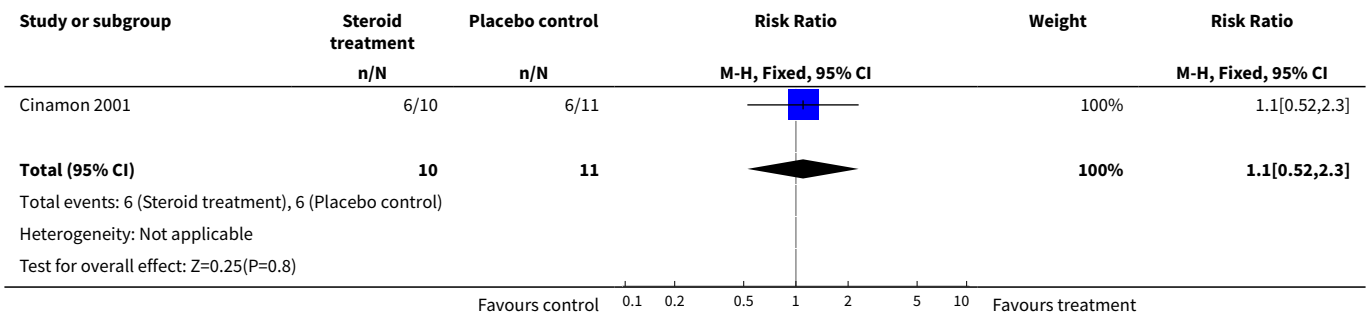
ATP: adenosine-5'-triphosphate
HBO: hyperbaric oxygen
SSHL: sudden sensorineural hearing loss
ISSHL: idiopathic sudden sensorineural hearing loss

DATA AND ANALYSES

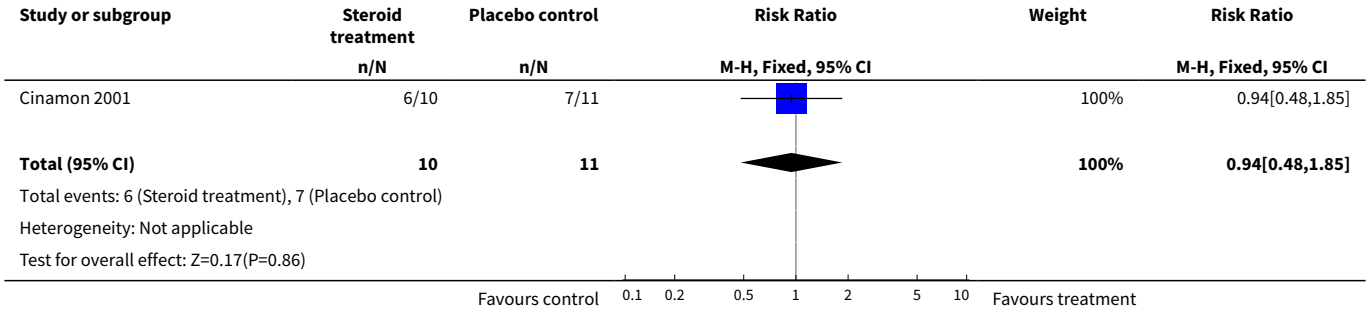
Comparison 1. Oral steroid versus oral placebo immediately post-treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hearing recovery: average speech frequencies (500, 1000, 2000 Hz)	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.52, 2.30]
2 Hearing improvement: average hearing level at six frequencies (250 to 8000 Hz)	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.85]
3 Hearing improvement: high-tone hearing level average (4000, 8000 Hz)	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.32, 2.39]

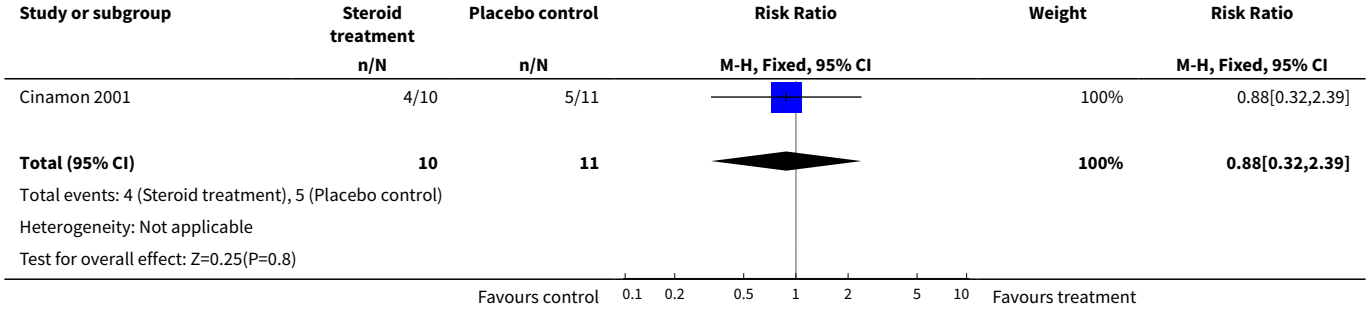
Analysis 1.1. Comparison 1 Oral steroid versus oral placebo immediately post-treatment, Outcome 1 Hearing recovery: average speech frequencies (500, 1000, 2000 Hz).



Analysis 1.2. Comparison 1 Oral steroid versus oral placebo immediately post-treatment, Outcome 2 Hearing improvement: average hearing level at six frequencies (250 to 8000 Hz).



Analysis 1.3. Comparison 1 Oral steroid versus oral placebo immediately post-treatment, Outcome 3 Hearing improvement: high-tone hearing level average (4000, 8000 Hz).

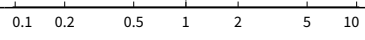


Comparison 2. Oral steroid versus oral placebo at follow-up (14 to 90 days, average 33 days)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hearing improvement: average speech frequencies (500, 1000, 2000 Hz)	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.56, 1.66]
2 Hearing improvement: average hearing level at six frequencies (250 to 8000 Hz)	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.64, 1.48]
3 Hearing improvement: high-tone hearing level average (4000, 8000 Hz)	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.52, 2.30]

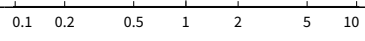
Analysis 2.1. Comparison 2 Oral steroid versus oral placebo at follow-up (14 to 90 days, average 33 days), Outcome 1 Hearing improvement: average speech frequencies (500, 1000, 2000 Hz).

Study or subgroup	Steroid treatment n/N	Placebo control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinamon 2001	7/10	8/11		100%	0.96[0.56,1.66]
Total (95% CI)	**10**	**11**		**100%**	**0.96[0.56,1.66]**
Total events: 7 (Steroid treatment), 8 (Placebo control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					

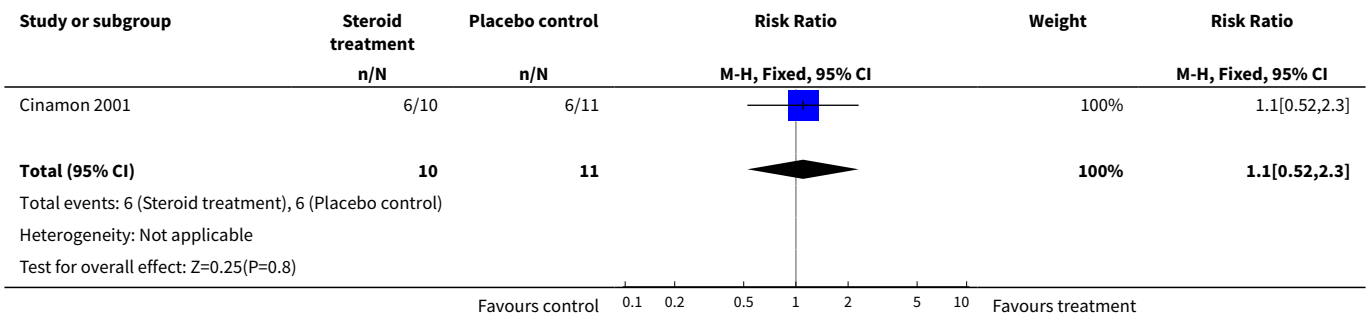


Analysis 2.2. Comparison 2 Oral steroid versus oral placebo at follow-up (14 to 90 days, average 33 days), Outcome 2 Hearing improvement: average hearing level at six frequencies (250 to 8000 Hz).

Study or subgroup	Steroid treatment n/N	Placebo control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinamon 2001	8/10	9/11		100%	0.98[0.64,1.48]
Total (95% CI)	**10**	**11**		**100%**	**0.98[0.64,1.48]**
Total events: 8 (Steroid treatment), 9 (Placebo control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.11(P=0.92)					



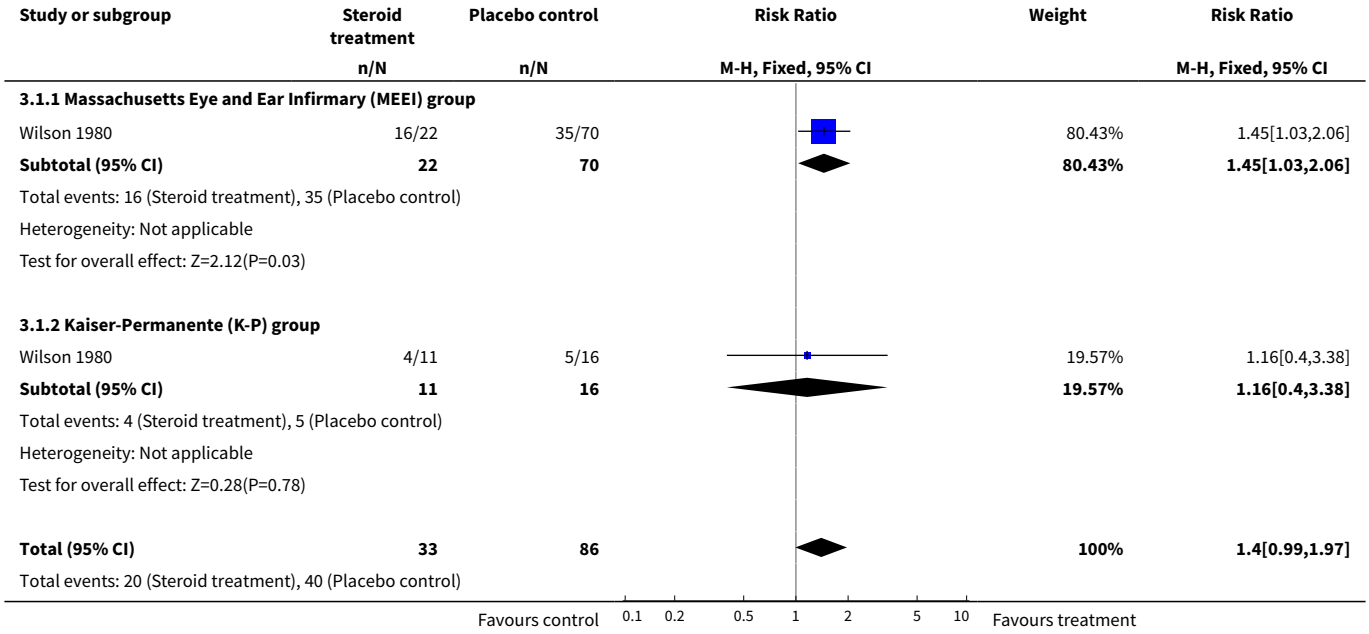
Analysis 2.3. Comparison 2 Oral steroid versus oral placebo at follow-up (14 to 90 days, average 33 days), Outcome 3 Hearing improvement: high-tone hearing level average (4000, 8000 Hz).

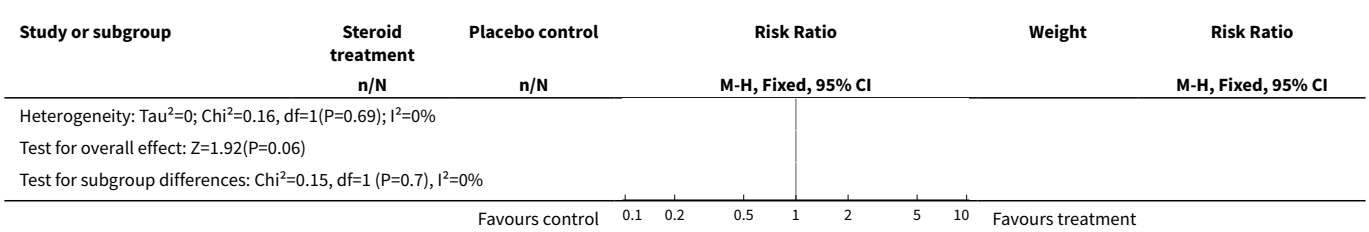


Comparison 3. Oral steroid versus oral placebo (4 weeks and 3 months follow-up)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hearing recovery (see 'Description of studies' for definition)	1	119	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.99, 1.97]
1.1 Massachusetts Eye and Ear Infirmary (MEEI) group	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.03, 2.06]
1.2 Kaiser-Permanente (K-P) group	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.40, 3.38]

Analysis 3.1. Comparison 3 Oral steroid versus oral placebo (4 weeks and 3 months follow-up), Outcome 1 Hearing recovery (see 'Description of studies' for definition).

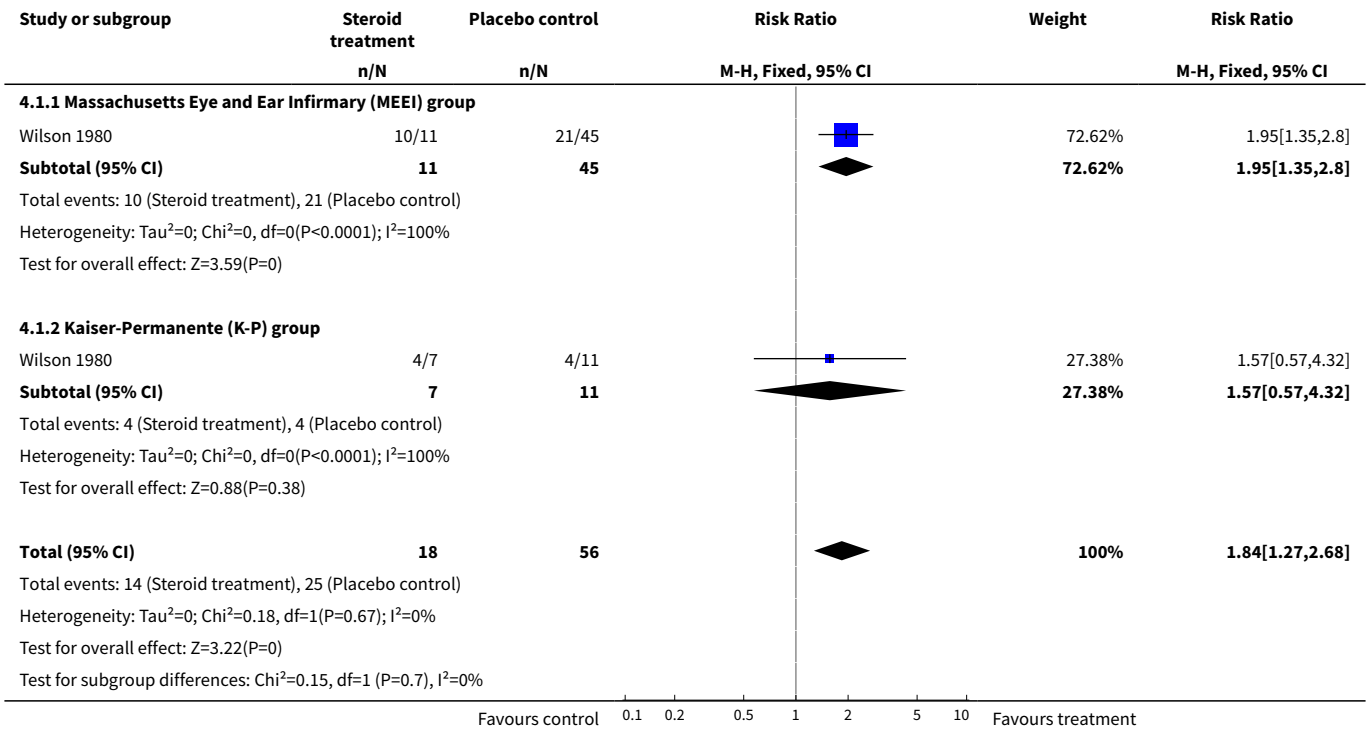




Comparison 4. Recovery by group for steroid-effective zone patients only (see 'Results' section)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Hearing recovery (see 'Description of studies' for definition)	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [1.27, 2.68]
1.1 Massachusetts Eye and Ear Infirmary (MEEI) group	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.35, 2.80]
1.2 Kaiser-Permanente (K-P) group	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.57, 4.32]

Analysis 4.1. Comparison 4 Recovery by group for steroid-effective zone patients only (see 'Results' section), Outcome 1 Hearing recovery (see 'Description of studies' for definition).

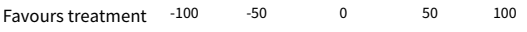


Comparison 5. Prednisolone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hearing improvement 8 days after treatment	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-11.73, 9.93]
2 Hearing improvement 3 months after diagnosis of SSHL	1	93	Mean Difference (IV, Fixed, 95% CI)	3.90 [-8.57, 16.37]

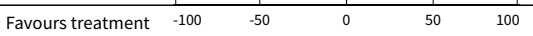
Analysis 5.1. Comparison 5 Prednisolone versus placebo, Outcome 1 Hearing improvement 8 days after treatment.

Study or subgroup	Prednisolone N	Prednisolone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nosrati-Zarenoe 2012	47	25.5 (27.1)	46	26.4 (26.2)		100%	-0.9[-11.73,9.93]
Total ***	**47**		**46**			**100%**	**-0.9[-11.73,9.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.16(P=0.87)							



Analysis 5.2. Comparison 5 Prednisolone versus placebo, Outcome 2 Hearing improvement 3 months after diagnosis of SSHL.

Study or subgroup	Prednisolone N	Prednisolone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nosrati-Zarenoe 2012	47	39 (20.1)	46	35.1 (38.3)		100%	3.9[-8.57,16.37]
Total ***	**47**		**46**			**100%**	**3.9[-8.57,16.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.61(P=0.54)							



APPENDICES

Appendix 1. Search strategies

PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
#1 "HEARING LOSS, SUDDEN" [Mesh] #2 "HEARING LOSS, SENSORINEURAL" [Mesh] #3 sudden* [tiab] #4 #2 AND #3	1 Sudden Deafness/ 2 Perception Deafness/ 3 sudden*.tw. 4 3 and 2	S1 (MH "Hearing Loss, Sensorineural") S2 TX hearing OR deaf* S3 TX sudden* S4 S1 or S2 S5 S3 and S4

(Continued)

#5 sshl [tiab] OR snhl [tiab] OR ishl [tiab] OR isshl [tiab] OR issnhl [tiab] OR ssnhl [tiab] OR (sudden [tiab] AND hearing [tiab]) OR (sudden [tiab] AND deaf* [tiab])
#6 #1 OR #4 OR #5
#7 "STEROIDS" [Mesh]
#8 "ANTI-INFLAMMATORY AGENTS" [Mesh]
#9 "ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL" [Mesh]
#10 #8 NOT #9
#11 "GLUCOCORTICOIDS" [Mesh]
#12 "Hydroxycorticosteroids"[Mesh]
#13 steroid* [tiab] OR corticosteroid* [tiab] OR glucocorticoid* [tiab] OR corticoid*
#14 beclomethason* [tiab] OR beclamet [tiab] OR beclocort [tiab] OR beclometasone [tiab] OR becotide [tiab] OR budesonide [tiab] OR betamethason* [tiab] OR betametasone [tiab] OR betadexamethasone [tiab] OR flubenisolone [tiab] OR hydrocortison* [tiab] OR cortisol [tiab] OR celesto* [tiab] OR cortisone [tiab]
#15 dexamethason* [tiab] OR dexamethason* [tiab] OR hexadecadrol [tiab] OR decadron [tiab] OR dexasone [tiab] OR hexadrol [tiab] OR horacort [tiab] OR pulmicort [tiab] OR rhinocort [tiab] OR methylfluorprednisolone [tiab] OR methylprednisolone [tiab] OR prednisolone [tiab] OR prednisone [tiab] OR flunisolid* [tiab] OR nasalide [tiab] OR millicorten [tiab] OR [tiab] OR adexon [tiab]
#16 fluticason* [tiab] OR flonase [tiab] OR flounce [tiab] OR mometason* [tiab] OR nasonex [tiab] OR fludrocortisone [tiab] OR triamclinolon* [tiab] OR nasacort [tiab] OR tri next nasal [tiab] OR aristocort [tiab] OR volon [tiab]
#17 #7 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18 #6 AND #17

5 (sshl or snhl or ishl or isshl or issnhl or ssnhl or (sudden* and hearing) or (sudden* and deaf*)).tw.
6 4 or 1 or 5
7 exp Steroid/
8 exp Antiinflammatory Agent/
9 exp Nonsteroid Antiinflammatory Agent/
10 8 not 9
11 exp Steroid Hormone/
12 (steroid* or corticosteroid* or glucocorticoid* or corticoid*).tw.
13 (beclomethason* or beclamet or beclocort or beclometasone or becotide or budesonide or betamethason* or betametasone or betadexamethasone or flubenisolone or hydrocortison* or cortisol or celesto* or cortisone).tw.
14 (dexamethason* or dexamethason* or hexadecadrol or decadron or dexasone or hexadrol or horacort or pulmicort or rhinocort or methylfluorprednisolone or methylprednisolone or prednisolone or prednisone or flunisolid* or nasalide or millicorten or adexon).tw.
15 (fluticason* or flonase or flounce or mometason* or nasonex or fludrocortisone or triamclinolon* or nasacort or tri next nasal or aristocort or volon).tw.
16 11 or 7 or 13 or 10 or 12 or 15 or 14
17 6 and 16

S6 TX sshl OR snhl OR ishl OR isshl OR issnhl OR ssnhl
S7 S5 or S6
S8 (MH "Steroids") or (MH "Antiinflammatory Agents, Steroidal")
S9 (MH "Antiinflammatory Agents, Non-Steroidal")
S10 s8 NOT s9
S11 TX steroid* or corticosteroid* or glucocorticoid* or corticoid*
S12 TX beclomethason* or beclamet or beclocort or beclometasone or becotide or budesonide or betamethason* or betametasone or betadexamethasone or flubenisolone or hydrocortison* or cortisol or celesto* or cortisone
S13 TX dexamethason* or dexamethason* or hexadecadrol or decadron or dexasone or hexadrol or horacort or pulmicort or rhinocort or methylfluorprednisolone or methylprednisolone or prednisolone or prednisone or flunisolid* or nasalide or millicorten or adexon
S14 TX fluticason* or flonase or flounce or mometason* or nasonex or fludrocortisone or triamclinolon* or nasacort or tri next nasal or aristocort or volon
S15 S10 or S11 or S12 or S13 or S14
S16 S7 and S15

Web of Science (Web of Knowledge)	CENTRAL	CAB Abstracts (Ovid)
#1 TS=(sshl or snhl or ishl or isshl or issnhl or ssnhl or (sudden* and hearing) or (sudden* and deaf*)) #2 TS=(steroid* or corticosteroid* or glucocorticoid* or corticoid*) #3 TS=(beclomethason* or beclamet or beclocort or beclometasone or becotide or budesonide or betamethason* or betametasone or betadexamethasone or flubenisolone or hydrocortison* or cortisol or celesto* or cortisone) #4 TS=(dexamethason* or dexamethason* or hexadecadrol or decadron or dexasone or hexadrol or horacort or pulmicort or rhinocort or methylfluorprednisolone or methylprednisolone or prednisolone or	#1 MeSH descriptor HEARING LOSS, SUDDEN explode all trees #2 MeSH descriptor HEARING LOSS, SENSORINEURAL explode all trees #3 sudden* #4 #2 AND #3 #5 sshl OR snhl OR ishl OR isshl OR issnhl OR ssnhl OR (sudden* NEAR hearing) OR (sudden* NEAR deaf*) #6 #1 OR #4 OR #5 #7 MeSH descriptor STEROIDS explode all trees #8 MeSH descriptor ANTI-INFLAMMATORY AGENTS explode all trees #9 MeSH descriptor ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL explode all trees	1 (sshl or snhl or ishl or isshl or issnhl or ssnhl or (sudden and hearing) or (sudden and deaf*)).tw. 2 exp Antiinflammatory Agent/ 3 exp Steroid Hormone/ 4 (steroid* or corticosteroid* or glucocorticoid* or corticoid*).tw. 5 (beclomethason* or beclamet or beclocort or beclometasone or becotide or budesonide or betamethason* or betametasone or betadexamethasone or flubenisolone or hydrocortison* or cortisol or celesto* or cortisone).tw. 6 (dexamethason* or dexamethason* or hexadecadrol or decadron

(Continued)

prednisone or flunisolid* or nasalide or millicorten or adexon)
#5 TS=(fluticason* or flonase or flounce or mometason* or nasonex or fludrocortisone or triamclinolon* or nasacort or tri next nasal or aristocort or volon)
#6 #5 OR #4 OR #3 OR #2
#7 #6 AND #1

#10 #8 NOT #9
#11 MeSH descriptor GLUCOCORTICOIDS explode all trees
#12 MeSH descriptor Hydroxycorticosteroids explode all trees
#13 steroid* OR corticosteroid* OR glucocorticoid* OR corticoid*
#14 beclomethason* OR beclamet OR beclocort OR beclometasone OR becotide OR budesonide OR betamethason* OR betametasone OR betadexamethasone OR flubenisolone OR hydrocortison* OR cortisol OR celesto* OR cortisone
#15 dexamethason* OR dexamethason* OR hexadecadrol OR decadron OR dexasone OR hexadrol OR horacort OR pulmicort OR rhinocort OR methylfluorprednisolone OR methylprednisolone OR prednisolone OR prednisone OR flunisolid* OR nasalide OR millicorten OR adexon
#16 fluticason* OR flonase OR flounce OR mometason* OR nasonex OR fludrocortisone OR triamclinolon* OR nasacort OR tri NEXT nasal OR aristocort OR volon
#17 #7 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18 #6 AND #18

or dexasone or hexadrol or horacort or pulmicort or rhinocort or methylfluorprednisolone or methylprednisolone or prednisolone or prednisone or flunisolid* or nasalide or millicorten or adexon).tw.
7 (fluticason* or flonase or flounce or mometason* or nasonex or fludrocortisone or triamclinolon* or nasacort or tri next nasal or aristocort or volon).tw.
8 2 OR 3 OR 4 OR 5 OR 6 OR 7
9 1 AND 8

Note: There have been minor changes made to the search strategy in PubMed and CENTRAL. For details please contact the Trial Search Co-ordinator of the Cochrane Ear, Nose and Throat Disorders Group.

WHAT'S NEW

Date	Event	Description
8 May 2013	New citation required but conclusions have not changed	One new included study added to the review (Nosrati-Zarenoe 2012). No substantive changes made to the review conclusions.
22 April 2013	New search has been performed	New searches run.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 1, 2006

Date	Event	Description
6 July 2009	New search has been performed	New searches were conducted in June 2009. No new studies were included. Thirteen further studies were added to the 'Excluded studies' section.
26 October 2008	Amended	Converted to new review format.

Date	Event	Description
4 November 2005	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Current version:

Dr Benjamin Wei: lead author, searching for trials, study selection, data extraction, data analysis, design of review, study selection, 'Risk of bias' assessment, analysis and interpretation of data, and writing of review.

Ms Dimitra Stathopoulos: co-author; data extraction, 'Risk of bias' assessment.

Prof SJ O'Leary: co-author, study selection, data extraction, 'Risk of bias' assessment, analysis and interpretation of data, and writing and editing review.

Previous versions:

Ms Sherina Muribu: co-author, data extraction, quality assessment.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Bionics Institute and the Department of Otolaryngology, University of Melbourne, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have adopted the Cochrane 'Risk of bias' tool for the assessment of included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*therapeutic use]; Dexamethasone [therapeutic use]; Glucocorticoids [*therapeutic use]; Hearing Loss, Sensorineural [*drug therapy]; Hearing Loss, Sudden [*drug therapy]; Methylprednisolone [therapeutic use]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans