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[Intervention Review]

Vasodilators and vasoactive substances for idiopathic sudden sensorineural hearing loss

Lekha Agarwal[1], David D Pothier[2]

[1]ENT Department, Russells Hall Hospital, Dudley, UK. [2]Department of Otolaryngology, Head and Neck Surgery, Toronto General Hospital, University Health Network, Toronto, Canada

Contact address: Lekha Agarwal, ENT Department, Russells Hall Hospital, Pensnett Road, Dudley, West Midlands, DY1 2HQ, UK. lekhaagr@yahoo.com, lekhaagr@doctors.org.uk.

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ABSTRACT

Background

Idiopathic sudden sensorineural hearing loss (ISSHL) is sudden hearing loss where clinical assessment fails to reveal a cause. The most widely used therapeutic agents for ISSHL are antivirals, steroids, hyperbaric oxygen, vasodilators and rheological/vasoactive substances. There is currently conflicting evidence for vasodilator and vasoactive substances in the treatment of ISSHL.

Objectives

1. To determine the effectiveness of vasodilators and other vasoactive substances in improving hearing in patients with ISSHL.
2. To determine the adverse effects of these medications.

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PubMed; EMBASE; CINAHL; Web of Science; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. The date of the most recent search was 16 September 2008.

Selection criteria

Randomised controlled trials (RCTs) of vasodilators/vasoactive substance versus placebo in the treatment of ISSHL. Trials were assessed for methodological quality.

Data collection and analysis

The authors assessed trials and extracted data independently. We contacted investigators to obtain additional information where necessary. Meta-analysis was neither possible nor considered appropriate due to the differences in the type of vasodilators used, dosage and duration of treatment. The quality and the result of each study was analysed and reported individually.

Main results

Only three trials, involving 189 participants, satisfied the inclusion criteria and these were of low methodological quality. One study showed a significant difference in hearing recovery in the vasodilator group (carbogen combined with a course of several other drugs) compared to the control group (a course of several other drugs alone). Another study only showed a significant improvement in higher frequencies in the vasodilator group (prostaglandin E1 + steroid) compared with the control group (placebo and steroid), no difference having been shown in overall hearing gain. In the third study the vasodilator group (naftidrofuryl and low-molecular weight dextran) showed an improvement only in lower frequencies over the control group (placebo and low-molecular weight dextran).

Two of the studies reported adverse effects from vasodilator treatment, whereas there was no mention of any side effects in the third. Five patients in one study developed a sensation of heaviness in the head which settled spontaneously and did not interfere with treatment. In the other study one patient developed an allergic reaction and had to be excluded from the study.

Authors' conclusions

The effectiveness of vasodilators in the treatment of ISSHL remains unproven. The included studies were of relatively poor quality and the number of patients included was small. Moreover, there were differences in the type, dosage and duration of vasodilator used in each study. Due to the degree of heterogeneity the results could not be combined to reach a conclusion.

PLAIN LANGUAGE SUMMARY

Vasodilators and vasoactive substances for idiopathic sudden sensorineural hearing loss

Idiopathic sudden sensorineural hearing loss (ISSHL) is sudden hearing loss where clinical assessment fails to reveal a cause. Hearing loss may vary from partial to total loss, and is usually accompanied by tinnitus. It has been frequently considered that ISSHL may have a vascular origin (i.e. is related to the blood circulatory system) and vasodilators and rheological substances are widely used as treatments. Vasodilators are drugs which widen blood vessels and thus improve blood flow. Vasoactive/rheological substances increase flow through blood vessels in other ways (such as by altering the viscosity of fluid). We found three trials, involving 189 participants, which showed improvement in hearing thresholds in those treated with vasodilators compared to control groups. However, as the number of patients included in the studies was small, and there were differences in the type, dosage and duration of vasodilator treatment used in each of these studies, the results could not be combined to reach a conclusion. The effectiveness of vasodilators in the treatment of ISSHL could not be proven. Further research is needed.

BACKGROUND

Sudden sensorineural hearing loss (SSHL) can be defined as an abrupt or rapidly progressing hearing loss of at least 30 dB in at least three contiguous frequencies over a period of no more than three days (Shambaugh 1990). Idiopathic sudden sensorineural hearing loss (ISSHL) is sudden hearing loss where clinical assessment fails to reveal a cause (Gates 2000). The incidence of ISSHL is approximately 8 to 15 per 100,000 persons per year (Hughes 1996; Stokroos 1996). The median age of patients presenting with ISSHL is between 40 and 54 years and there is an equal preponderance of the disease in both sexes. Most of these cases are unilateral, that is involving one side, and right and left ears have an equal chance of being affected. Bilateral cases are uncommon and are more likely to be associated with serious systemic disease (Gates 2000).

The clinical patterns of ISSHL are quite variable. Hearing loss may vary from partial to total loss, and is usually accompanied by tinnitus. The vestibular system is involved in 30% to 40% of cases, and these patients may also experience dizziness or vertigo. Partial or complete spontaneous recovery occurs in 50% to 65% of cases (Gates 2000).

The aetiology of ISSHL remains obscure. Different theories include disturbance of cochlear blood flow, viral infections, autoimmune disease, Reissner's membrane rupture or a combination of such mechanisms (Cole 1988; Shikowitz 1991; Thurmond 1998).

The clinical challenge in the care of a patient with sudden sensorineural hearing loss is to determine a specific cause of the hearing loss. In most cases there is no obvious cause and few clues arise from the history, physical examination or audiometric testing, which are the minimal elements of the clinical assessment. Most cases will require further investigations in the form of CT or MRI scanning to exclude other causes of sensorineural hearing loss such as lesions of the eighth cranial nerve.

Treatment selection should ideally be based on the cause (Mattox 1980). Since the cause is often unknown, most studies have involved a multimodal treatment strategy based on the assumption that one or more medications or techniques will reverse the pathophysiologic changes in the auditory system. This empiric strategy has the advantage that at least one effective treatment may be provided to the patient, but has the drawback of obscuring the effect of any single treatment, as well as exposing the patient to the side effects of a number of different treatments. Evaluation of treatments has been further hampered by the low incidence of ISSHL and the tendency for hearing to recover spontaneously (in up to 65% of cases) (Mattox 1989).

The most widely used therapeutic agents for ISSHL are antivirals, steroids, hyperbaric oxygen, vasodilators and rheological/ vasoactive substances. Other drugs, such as intravenous contrast agents (Hypaque), calcium channel blockers, prostaglandin E1 infusion and ethacrynic acid, have been assessed in clinical studies. Interferon alpha and acyclovir have been used as antiviral agents. Steroids are anti-inflammatory drugs which are presumed to suppress inflammatory changes such as cellular infiltration and tissue oedema, limitation of which increases tissue perfusion. Hyperbaric oxygen improves the oxygenation of the inner ear and thereby improves hearing and/or reduces the intensity of tinnitus.

It has been frequently postulated that ISSHL has a vascular origin and vasodilators and rheological substances are widely used. Vasodilators increase the calibre of blood vessels and thus improve blood flow, whereas vasoactive/rheological substances increase flow through blood vessels by other mechanisms, such as altering the viscosity of fluid. It has been demonstrated in animals that cochlear function is sensitive to changes in microcirculation, and that even limited impairment of perfusion leads to immediate loss of function of the organ of Corti (Miller 1988). The vascular theories of ISSHL describe a spectrum of putative pathophysiologic alterations at the capillary and microvascular levels. They include embolism, blood sludging, hypercoagulability, vasospasm, intracochlear haemorrhage, arteriosclerosis, systemic vascular disease and connective tissue disorders. Blood supply to the inner ear is provided by the labyrinthine artery which is a functional end artery, that is it has no collateral vessels and thus shunting from the periphery cannot compensate for disturbances of blood flow to the inner ear (Suckfull 2002). Furthermore, the labyrinthine artery supplies the vestibulocochlear artery and the spiralis modiolus artery, which supply the cochlea and the vestibular organ. The fact that most cases of ISSHL are of very rapid onset lends support to the hypothesis that ISSHL has a vascular cause.

Oral vasodilators, such as papaverine or nicotinic acid, produce facial flushing and headache, but there is no evidence that cochlear blood flow is increased (Fisch 1976). The duration of treatment varies from days to months depending on the type of agent employed and the opinion of the prescriber (Laskawi 1987). Potential side effects can include allergy and pruritus (itching).

Cochrane Reviews of steroids and hyperbaric oxygen for the treatment of ISSHL have been published. The review of steroids concluded that the value of steroids in the treatment of idiopathic sudden sensorineural hearing loss remained unclear because the evidence obtained from randomised controlled trials was contradictory in outcome, in part because the studies were based on too small a number of patients (Wei 2006). The authors of the review of hyperbaric oxygen concluded that for people with early presentation of ISSHL, the application of hyperbaric oxygen therapy significantly improved hearing, but the clinical significance of the level of improvement was not clear (Bennett 2005).

There is currently conflicting evidence for vasodilator and vasoactive substances in the treatment of ISSHL. We therefore conducted a systematic review in order that the benefits of treatment could be weighed against any associated potential risk.

OBJECTIVES

1. To determine the effectiveness of vasodilators and other vasoactive substances in improving hearing in patients with ISSHL.
2. To determine the adverse effects of these medications.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

We included patients of any age with an idiopathic sudden sensorineural hearing loss (ISSHL) and treated with vasodilators and/or vasoactive substances. Patients had to fit the following entry criteria.

ISSHL was defined as:

1. a history of a sudden decrease in hearing;
2. hearing loss of at least 30 dB with no air-bone gap;
3. unilateral or bilateral hearing loss;
4. 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;
5. no other neurological signs exist except the eighth cranial nerve defect.

Exclusion criteria included:

1. all other types of sensorineural hearing loss, or conductive forms of hearing impairment;
2. a history of fluctuating sensorineural hearing loss;
3. patients who had a cause for their sudden sensorineural hearing loss such as noise, head injury, drugs etc.

Types of interventions

We included studies of vasodilators of any type regardless of dosage compared to placebo or no treatment. We grouped and analysed studies separately according to the comparisons made.

1. Vasodilator versus placebo.
2. Vasodilator versus no treatment.
3. (Vasodilator + other treatment) versus (placebo + same other treatment).
4. (Vasodilator + other treatment) versus (same other treatment).
5. Vasoactive substances versus placebo.
6. Vasoactive substances versus no treatment.
7. (Vasoactive substances + other treatment) versus (placebo + same other treatment).
8. (Vasoactive substances + other treatment) versus (same other treatment).

Types of outcome measures

Primary

The proportion of patients whose hearing recovered:

1. completely;
2. partially;
3. by more than 10 dB across an average of speech frequencies;
4. to a threshold of less than or equal to 30 dB in speech frequencies (0.5, 1, 2, 4 kHz);
5. to less than or equal to 15 dB of the other ear.

We aimed to determine whether these improvements were short-term or long-term.

Secondary

Evaluation of the side effects of these treatment modalities.

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 16 September 2008.

Electronic searches

We searched the following resources for published and unpublished trials:

- the Cochrane Ear, Nose and Throat Disorders Group Trials Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 3, 2008);
- PubMed;
- EMBASE;
- CINAHL;
- LILACS;
- KoreaMed;
- IndMed;
- PakMediNet;
- Web of Science;
- BIOSIS Previews;
- *m*RCT (Current Controlled Trials);
- NRR (National Research Register) archive; and
- Google.

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 5.0.1, Box 6.4.b. (Handbook 2008)). Search strategies for key databases including CENTRAL and PubMed are shown in Appendix 1.

Searching other resources

We scanned reference lists of identified studies for further trials and contacted authors for clarification as necessary. We searched PubMed, TRIPdatabase, NHS Evidence - ENT and audiology 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

One author scanned the initial search results to identify trials that loosely met the inclusion criteria. The two authors then reviewed the full text articles of the retrieved trials and applied the inclusion criteria independently. Any differences of opinion regarding inclusion were resolved by discussion. RevMan 5.0 was used to compile the review (RevMan 2008).

Risk of bias assessment

The two review authors independently assessed the risk of bias of all included trials, and resolved any differences in opinion by discussion. We used a modification of the method used by Chalmers 1990 to assess for the following characteristics:

1. number of participants and the power of the study;
2. adequacy of randomisation;
3. allocation concealment;
4. blinding of patients, providers and outcome assessors;
5. losses to follow up;
6. quality of the outcome assessment.

We graded studies A, B or C for their overall risk of bias, where:

A = minimisation of bias in all of the above categories;
B = each of the criteria in A partially met;
C = one or more of the criteria in A not met.

Although we intended to use study quality for sensitivity analysis, the studies were not combined.

Data extraction

The authors extracted data independently onto standardised data forms. We compared the extracted data and resolved disagreements by discussion. We contacted authors if any point required clarification or if data were missing.

Data analysis

We compared the effects of different types of vasodilator. We extracted the data for an intention-to-treat analysis to include all randomised patients with ISSHL. As the data were not comparable, we did not combine to give a summary measure of effect.

RESULTS

Description of studies

Of the 154 abstracts retrieved from our search, we excluded 133 as these were not focused on ISSHL or the treatment was not primarily vasodilators. We examined the remaining 21 studies in detail and of these three studies were included in the review. The three studies which fulfilled our inclusion criteria were Ogawa 2002, Poser 1992 and Ni 2004.

Excluded studies

We excluded 18 studies (Ahn 2005; Ahn 2006; Cesarone 2002; Cinamon 2001; Desloovere 1989; Dubreuil 1986; Fisch 1983; Friedrich 1991; Giger 1979; Gutman 1995; Hoffmann 1994; Kallinen 1997; Kanzaki 2003; Kronenberg 1992; Lenarz 1989; Mann 1986; Nakashima 1989; Reisser 2001) as they did not meet the inclusion criteria for the review. The reasons for exclusion of studies are set out in the table 'Characteristics of excluded studies'.

Included studies

Ogawa 2002, Poser 1992 and Ni 2004 were the three studies included in the review and involved a total of 189 participants. The vasodilators/vasoactive agents used in the studies were prostaglandin E1 (a prostanoid with vasodilator properties), naftidrofuryl and carbogen (5% CO_2 and 95% O_2) respectively. Details of the methods, participants, interventions and outcomes are summarised in the 'Characteristics of included studies' table. The two authors critically reviewed the three included randomised controlled trials to assess their methodological quality. All three were graded C as their overall methodological quality was low.

Ogawa 2002

This was a prospective, double blind, randomised controlled study to evaluate the effectiveness of prostaglandin E1 on idiopathic sudden sensorineural hearing loss. Either prostaglandin E1 or placebo was used in addition to a steroid in each group. Fifty-seven adults (aged 20 to 68 years) with ISSHL participated in the study. The inclusion criterion was a diagnosis of idiopathic sudden hearing loss of at least an average of 40 dB in the frequencies 250 Hz to 4 kHz, of not more than two weeks duration. There were 39 males and 18 females in the study.

The two interventions in the study were:

Group 1: 60 mcg prostaglandin E1 given as a continuous infusion and 100 mg hydrocortisone;

Group 2: placebo given as a continuous infusion and 100 mg hydrocortisone.

The duration of treatment in both groups was one week. The outcome was evaluated one to two months after treatment using pure tone audiometry (PTA). A 'complete recovery' was defined as a hearing threshold in all five frequencies </= 20 dB, or improvement to the same degree as the unaffected ear. A 'remarkable improvement' was PTA improvement of > 30 dB. 'Improvement' was defined as PTA improvement of 10 to 30 dB. 'No change or deterioration' was defined as PTA improvement of < 10 dB.

Ni 2004

This was a prospective, single blind, randomised controlled study to evaluate the effect of carbogen on idiopathic sudden sensorineural hearing loss.

Fifty-two patients (aged 12 to 66 years) with ISSHL participated in the study. The inclusion criterion was a diagnosis of idiopathic sudden hearing loss; the diagnostic criteria for this were not mentioned, but both groups had similar audiometric data, with the study group PTA average of 75 dB and the control group 76 dB. All participants were investigated with pure tone audiometry, impedance audiometry and CT scan to rule out acoustic neuroma.

The two interventions in the study were:

Group 1: carbogen and drug course (IV dexamethasone + vitamin B + low-molecular weight dextran + salvise miltiorrhiaze + oral intake of vitamin C + vitamin E); carbogen inhalation for 30 minutes, 30 minutes break followed by another 30 minutes of inhalation;

Group 2: drug course only.

The average duration of treatment was three weeks. The outcome was evaluated using pure tone audiometry after treatment. A ‘complete recovery’ was defined as attaining normal hearing in the frequency range 0.25 to 4 kHz. A ‘significant’ recovery was hearing improvement greater than 30 dB in the frequency range 0.25 to 4 kHz. ‘Some recovery’ was hearing improvement between 15 and 30

dB in the frequency range 0.25 to 4 kHz. 'No recovery' was hearing improvement less than 15 dB in the frequency range 0.25 to 4 kHz.

Poser 1992

This was a prospective, double blind, randomised controlled study to evaluate the effectiveness of naftidrofuryl and low molecular weight dextran on idiopathic sudden sensorineural hearing loss. The study was conducted at at the ENT clinic of the Zentralkrankenhaus, St-Juergen-Strasse, Bremen, Germany. Eighty patients with a diagnosis of ISSHL participated in the study. The inclusion criterion was a diagnosis of single sided ISSHL which had existed for no longer than 10 days.

The two interventions in the study were:

Group 1: nmlD group (monotherapy with low-molecular weight dextran and placebo). This was administered according to the following regime, in which each infusion lasted three hours:

Day 1 to 3: two infusions with 500 ml 10% nmlD, middle-molecular weight dextran (40,000);

Day 4 to 10: one infusion with 500 ml nmlD.

Group 2: nmlD and NA group (monotherapy with low-molecular weight dextran and naftidrofuryl). This was administered according to the following regime of similar duration:

Day 1 to 3: two infusions with 500 ml nmlD and 600 mg naftidrofuryl each, and three times 200 mg naftidrofuryl orally in retard form;

Day 4 to 10: one infusion with 500 ml nmlD and 600 mg naftidrofuryl each, and three times 200 mg naftidrofuryl orally in retard form.

The outcome measured was audiometric improvement.

Risk of bias in included studies

There was some risk of bias in the included studies as depicted in the 'Characteristics of included studies' table. Allocation concealment was adequate in two studies (Ogawa 2002; Poser 1992), and allocation could be concealed up to the point of assignment of treatment in the third study (Ni 2004). The patients in all the three studies were randomly assigned to treatment and control group. The exact method used to randomise patients and how blinding was achieved were not clearly stated. The drugs used in both the treatment and control group were identical in appearance in the Ogawa 2002 and Poser 1992 studies. In the Ni 2004 study, carbogen was used in the treatment group and hence allocation could be concealed up to the point of assignment of treatment. There was also risk of bias in the included studies because the number of patients in each study was small.

Effects of interventions

No conclusions can be drawn about the effectiveness, or lack thereof, of vasodilators in the treatment of idiopathic sudden sensorineural hearing loss. Meta-analysis was neither possible nor considered appropriate due to the differences in the type of vasodilators used, dosage and duration of treatment.

The results of the individual studies are as follows.

Ogawa 2002

The results of Ogawa 2002 did not show a beneficial effect of prostaglandin E1 (PGE1) on the treatment of ISSHL. No significant differences were observed in overall hearing gain or in the rate of hearing improvement between the PGE1 and the placebo group.

Marked hearing improvement was seen in 66.7% of the PGE1 group as compared to 64.3% of the control group. There was a significant difference between the treatment and control groups in the higher frequencies. Marked hearing improvement at 4 kHz was found in 48% of the PGE1 and 28% of the control group. At 8 kHz marked improvement was found in 68% of the PGE1 group compared to 36% of the placebo group. Patients with severe tinnitus along with ISSHL had marked recovery in symptoms in the PGE1 group (44.4%) compared to placebo (12.5%).

Ni 2004

The results of Ni 2004 showed a statistically significant difference between treatment and control group. In the carbogen group, the proportion of patients whose hearing improved was 76.9% compared to 50% in the control group. The difference in the outcome between the two groups reached statistical significance ($P < 0.05$).

Poser 1992

In Poser 1992 there was a 70% improvement in the low frequencies in the dextran and naftidrofuryl group compared to 40% in the dextran monotherapy group. The differences in the higher frequencies were not clear.

D I S C U S S I O N

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

We used a sensitive search strategy to identify as many studies as possible for the treatment of ISSHL, to avoid selection bias. We used strict inclusion criteria to retain studies which were less likely to be biased.

Of the 147 abstracts retrieved from our search, 14 studies were examined in detail of which only three randomised controlled trials were included in the review. The three studies which fulfilled our inclusion criteria were Ogawa 2002, Poser 1992 and Ni 2004.

Ogawa 2002 showed marked hearing improvement in higher frequencies and significant improvement in tinnitus in the PGE1 group compared to placebo (44% versus 13%), but there were no significant differences in the overall hearing gain or in the rate of hearing improvement between the PGE1 and the placebo group.

Ni 2004 showed a statistically significant difference between treatment and control group. In the carbogen group the proportion of patients whose hearing improved was 76.9% compared to 50% in the control group. The difference in the outcome between the two groups reached statistical significance ($P < 0.05$).

Poser 1992 showed marked improvement in the low frequencies in the dextran and naftidrofuryl group compared to the dextran monotherapy group (70% versus 40%). The differences in the higher frequencies were not clear.

The included studies were of relatively poor quality and the number of patients included in the studies was small. Moreover there were differences in the type, dosage and duration of vasodilator treatment used in each of these studies. Due to the degree of heterogeneity the results could not be combined to reach a conclusion. Also there were differences in the definition of hearing improvement, the geographical background of participants and outcome assessment in each of the three included studies.

The natural history of ISSHL is highly variable probably because its pathogenesis is multifactorial. Spontaneous recovery also frequently occurs thus making it difficult to determine the outcome of studies.

AUTHORS' CONCLUSIONS

Implications for practice

There is no good evidence to support the effectiveness, or lack thereof, of vasodilators in the treatment of ISSHL. The incidence of side effects and the cost of vasodilator treatment for ISSHL still need to be determined.

Implications for research

There is need for more randomised controlled trials in the future involving larger numbers of participants so that firm conclusions can be drawn from them. More data are needed on this subject. This would require a large, well-designed randomised controlled trial to give adequate power and avoid the problems noted in this review. Future researchers should refer to the CONSORT statement (Moher 2001) while designing and reporting their randomised controlled trials, so that they meet a uniform international standard.

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CHARACTERISTICS OF STUDIES

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

Ni 2004

Methods	Double blind, randomised controlled trial
Participants	52 patients (aged 12 to 66 years), randomly assigned to 2 different treatment groups. Gender data were unavailable.
Interventions	Group 1: carbogen and drug course (IV dexamethasone + vitamin B + LMW dextran + salvise miltiorrhiaze + oral intake of vitamin C + vitamin E); carbogen inhalation for 30 minutes, 30 minutes break followed by another 30 minutes of inhalation Group 2: drug course only
Outcomes	1. Complete recovery: normal hearing in 0.25 to 4 kHz frequency range 2. Significant recovery: > 30 dB in 0.25 to 4 kHz frequency range 3. Some recovery: 15 to 30 dB in 0.25 to 4 kHz frequency range The proportion of patients who had some degree of recovery was 76.9% in group 1 (treatment) and in group 2 (control) was 50 %. The difference in outcome between the 2 groups reached statistical significance (P < 0.05).
Notes	Adverse effects: 5 patients in group 1 (treatment, carbogen) complained of a sensation of swelling in the area of the head, which settled spontaneously and did not interfere with their treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Allocation concealment up to the point of assignment

Ogawa 2002

Methods	Double blind, randomised controlled trial
Participants	57 adults (aged 20 to 68 years), 39 male and 18 female, randomly assigned to 2 different treatment groups
Interventions	Group 1: the patients in the PGE1 group received a continuous infusion containing 60 mcg PGE1 and 100 mg hydrocortisone Group 2: the placebo group were treated with a continuous infusion of an inactive placebo and 100 mg hydrocortisone
Outcomes	1. Complete recovery - all 5 frequencies of final audio </= 20 dB 2. Remarkable improvement: PTA improvement > 30 dB 3. Improvement: PTA improvement is 10 to 30 dB 4. No change or deterioration: PTA improvement is < 10 dB

Ogawa 2002 *(Continued)*

	No significant differences were observed in the improvements of pure tone average and subjective symptoms between PGE1 and placebo groups, however significant improvement was noted in higher frequencies and tinnitus (44% versus 13%)
Notes	No adverse effects were documented in the study

Poser 1992

Methods	Double blind, randomised controlled trial
Participants	80 patients randomly assigned to 2 different treatment groups. Age and gender data were unavailable.
Interventions	Group 1: monotherapy with low-molecular weight dextran and placebo Group 2: monotherapy with low-molecular weight dextran and naftidrofuryl
Outcomes	Outcome assessment was done by direct comparison of thresholds between groups In this study there was a 70% improvement in the low frequencies in the dextran and naftidrofuryl group, compared to 40% in the dextran monotherapy group. The differences in the higher frequencies were not clear.
Notes	One patient in the dextran monotherapy group was excluded from the study as he had a allergic reaction on day 4 of the treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	

ATP = adenosine triphosphate
HAES = hydroxyethyl starch
LMW = low-molecular weight
PGE1 = prostaglandin E1
PTA = pure tone audiometry

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

Study	Reason for exclusion
Ahn 2005	Allocation: Inadequate randomisation (patient's preference)
Ahn 2006	Allocation: Randomised (method of randomisation not clear) Participants: 270 patients with sudden sensorineural hearing loss of 30 dB in 3 contiguous frequencies. Patients were grouped as diabetic and non-diabetic and the study was designed to compare the hearing improvement in diabetics as compared to non-diabetics.
Cesarone 2002	Allocation:

Study	Reason for exclusion
	Randomised (method of randomisation not stated). 40 patients with peripheral vascular disease and unilateral hearing loss were randomly assigned to 2 groups. Treatment group was given pentoxyphylline and the other group was given a placebo. Participants: Patients only included arteriopaths
Cinamon 2001	Allocation: Inadequate randomisation (rotation)
Desloovere 1989	Allocation: According to day of admission. No clear control group.
Dubreuil 1986	Allocation: Randomised (by using a random number chart) Participants: 20 patients with sudden sensorineural hearing loss. Cases of idiopathic, noise-induced and pressure-induced deafness were included. Progressive or gradual onset deafness cases were excluded, as were those of bacterial, toxic, neoplasic or iatrogenic origins, those relating to a central neurological disorder and trauma cases (fracture of petrosal bone, foreign body, rupture of the eardrum). Those patients receiving treatments which could not be interrupted and which were likely to interfere with true evaluation of intervention efficacy were excluded. Interventions: Group 1: Ginkgo biloba extract (EGb) Group 2: nicergoline (alpha blocker)
Fisch 1983	Allocation: Randomised (by using a code) Participants: 46 patients with sudden hearing loss, none were found to have serologic evidence of acute infection (tested: *M. pneumoniae*, influenza A/B, parainfluenza, *Herpes simplex*, adenovirus, *H. varicellae*, CMV) Intervention: Group 1: IV infusion of papaverine hydrochloride and low molecular weight dextran Group 2: carbogen (95% oxygen and 5% CO_2)
Friedrich 1991	Allocation: Randomised (method of randomisation not clear) Participants: Patients with sudden hearing loss. Audiological data not stated. 40 patients (25 males; 15 females). Age range 52 to 67 years. Intervention: Group 1: HAES 10% Group 2: HAES 6%

Study	Reason for exclusion
Giger 1979	Allocation: Randomised (using a code) Participants: 55 patients with sudden idiopathic hearing loss. All patients had sudden hearing loss; none were found to have serologic evidence of acute infection (tested: *M. Pneumoniae*, influenza A/B, parainfluenza, *Herpes simplex*, *Adenoviridae*, *H. Zoster*, CMV) Interventions: Treatment group: oxycarbon (95% O_2 5% CO_2) Control group: intravenous therapy consisting of 900 mg eupaverin, 25 mg Soludacortin and 0.5 ml Liquemin in 1 litre of physiologic saline and Rheumacrodex 500 ml
Gutman 1995	Allocation: Randomised (method of randomisation not clear) Participants: 39 patients with acute tinnitus, with and without acute hearing loss. Patients with Ménière's, arrhythmias, hypertension, acute stroke and vascular disease were excluded. Interventions: Treatment group: 200 mg of naftidrofuryl hydrogen oxalate in 500 ml HAES 6% Control group: 12 g piracetam in 500 ml HAES 6%
Hoffmann 1994	Allocation: Randomised (by even versus odd admission days) Participants: 80 patients with untreated sudden hearing loss. Exclusion criteria: alcohol abuse, severe organ damage, on medication for increasing perfusion Intervention: Treatment group: 175 mg Gingko extract EGb 761 in 500 ml HAES 6% plus 160 mg as tablets Control group: 400 mg naftidrofuryl in 500 ml HAES 6% plus 400 mg as tablets
Kallinen 1997	Allocation: Randomised (method of randomisation not stated). 168 patients suffering from idiopathic sudden hearing loss were analysed in this study in the period 1982 to 1989. The study included 91 males and 77 females with a mean age of 51 years, ranging from 12 to 78 years. The patients were admitted to the hospital for idiopathic sudden hearing loss, and the treatment was started promptly. The patients were divided into 3 different treatment groups: group 1 was treated with anticoagulant therapy, group 2 received both anticoagulant therapy and carbogen (5% oxygen and 95% carbon dioxide) inhalation therapy, and group 3 was treated only with carbogen inhalation therapy. Participants: 3 groups with differing audiometric criteria Interventions: Anticoagulant versus carbogen
Kanzaki 2003	Allocation:

Study	Reason for exclusion
	Inadequate randomisation. Multi-centre study in which 6 drugs (ATP, betamethasone, hydrocortisone, beraprost sodium, PGE1 and amidotrizoate) were empirically selected. Each participating centre was assigned 2 drugs.
Kronenberg 1992	Allocation: Randomised (method of randomisation not stated). 27 patients with idiopathic sudden sensorineural hearing loss were randomly assigned to 2 groups. Treatment group (n = 13) and placebo group (n = 14). The patients age ranged from 21 to 79 years. Participants: Sudden hearing loss in at least 1 ear of at least 20 dB within 1 week of presentation Intervention: Procaine and low-molecular weight dextran versus placebo Outcome: Primary outcome measure not stated or calculable
Lenarz 1989	Allocation: Randomised (method of randomisation not stated). 80 patients with idiopathic sudden sensorineural hearing loss in the period 1986 to 1988 were randomly assigned to 2 treatment groups. Participants: - sudden single-sided hearing decline without vestibular involvement - sensory hearing hardness - possible vascular genesis - no other aetiologistical factors Intervention: HAES and naftidrofuryl versus nimodipine
Mann 1986	Allocation: Randomised (method of randomisation not stated). In this study 50 patients with idiopathic sudden sensorineural hearing loss were randomly assigned to 2 treatment groups. There were 26 males and 24 females in the study. The age of patients ranged from 26 to 65 years. Participants: Patients with sudden hearing loss without vestibular involvement. Duration not stated. Audiological criteria not stated. Interventions: Nifed versus naftidrofuryl
Nakashima 1989	Allocation: Inadequate randomisation (unclear methods and included retrospective data)
Reisser 2001	Allocation: Randomised (method of randomisation not stated). 72 patients with a diagnosis of idiopathic sudden hearing loss were randomly assigned to 2 treatment groups. The age ranged from 20 to 83 years. Allocation was concealed using computer software.

Study	Reason for exclusion
	Participants: Patients with sudden hearing loss of >/= 20 dB (30 dB average hearing loss over the frequency range 250 to 6000 Hz) with no evident cause Intervention: Pentoxifylline versus Ginkgo biloba

ATP = adenosine triphosphate
CMV = cytomegalovirus
HAES = hydroxyethyl starch
PGE1 = prostaglandin E1

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Datastar)
#1 VASODILATOR AGENTS explode all trees (MeSH) #2 vasodilat* OR vasoacti* #3 flunarizine OR betaserk OR pentoxifylli* OR betahistine OR nitric ADJ oxide OR prostaglandin OR lipoprostaglandin OR nylidrin OR papaverine OR nicotinic OR histamine OR atropine OR carbogen #4 naftidrofuryl* OR prostacyclin* OR nafronyl OR hydroxyethyl OR buflomedil* OR loftyl OR taprosten OR sadamine OR trimetazidine OR trental OR dusodril OR HES OR HAES #5 vincamine OR vincapront OR puerarin OR anisodamine OR flunaricine OR nimodipine OR xanitol OR nicotinate OR regeneresen OR vinpocetin #6 inosine OR isoprinosine OR hydralazine OR apresdine OR minoxidil OR loniten #7 fendiline OR felodipine OR adenosine OR lidoflazine OR vincamine OR tolazoline #8 acetylcholine OR alprostadil OR amiodarone OR amlodipine OR amrinone OR amyl ADJ nitrate OR bencyclane OR bepridil OR bradykinin OR calcitonin OR celiprolol OR chromonar OR cromakalim #9 cyclandelate OR diazoxide OR dihydroergo* OR dilazep OR diltiazem OR dipyridamole OR doxazosin OR dyphylline OR enoximone OR ergoloid OR erythrit* OR fendoldopam OR heptaminol OR hexobendine #10 iloprost OR isosorbide OR isoxsuprine OR isradipine OR kallidin OR khellin OR methylmethacrylate OR mibefradil OR milrinone #11 molsidomine OR moxisylyte OR niacin OR nicardipine OR nicergoline OR nicorandil OR nicotinyl OR nifedipine OR nimodipine OR nisoldipine OR nitrendipine OR nitroglycerin OR nitroprusside OR nonachlazine #12 oxprenolol OR oxyfedrine OR pentaerythritol OR perhexiline OR phenoxybenzamine OR pinacidil OR pindolol OR polymethyl OR prenylamine OR propranolol OR sodium ADJ azide OR suloctidil	#1 "Vasodilator Agents"[Mesh] #2 "Vasodilator Agents"[Pharmacological Action] #3 vasodilat* OR vasoacti* OR flunarizine OR betaserk OR pentoxifylli* OR betahistine OR "nitric oxide" OR prostaglandin OR lipoprostaglandin OR nylidrin OR papaverine OR nicotinic OR histamine OR #4 inosine OR isoprinosine OR hydralazine OR apresdine OR minoxidil OR loniten OR fendiline OR felodipine OR adenosine OR lidoflazine OR vincamine OR tolazoline OR acetylcholine OR alprostadil OR amiodarone OR amlodipine OR amrinone OR amyl ADJ nitrate OR bencyclane OR bepridil OR bradykinin OR calcitonin OR celiprolol OR chromonar OR cromakalim #5 cyclandelate OR diazoxide OR dihydroergo* OR dilazep OR diltiazem OR dipyridamole OR doxazosin OR dyphylline OR enoximone OR ergoloid OR erythrit* OR fendoldopam OR heptaminol OR hexobendine #6 iloprost OR isosorbide OR isoxsuprine OR isradipine OR kallidin OR khellin OR methylmethacrylate OR mibefradil	1. VASODILATOR-AGENT#.DE. 2. (vasodilat$3 OR vasoacti$3).TI,AB. 3. (flunarizine OR betaserk OR pentoxifylli$3 OR betahistine OR nitric ADJ oxide OR prostaglandin OR lipoprostaglandin OR nylidrin OR papaverine OR nicotinic OR histamine OR atropine OR carbogen).TI,AB. 4. (nafronyl OR naftidrofuryl$15 OR prostacyclin$1 OR hydroxyethyl OR buflomedil$13 OR loftyl OR taprosten OR sadamine OR trimetazidine OR trental OR dusodril OR HES OR HAES).TI,AB. 5. (vincamine OR vincapront OR puerarin OR anisodamine OR flunaricine OR nimodipine OR xanitol OR nicotinate OR regeneresen OR vinpocetin).TI,AB. 6. (inosine OR isoprinosine OR hydralazine OR apresdine OR minoxidil OR loniten).TI,AB. 7. (fendiline OR felodipine OR adenosine OR lidoflazine OR vincamine OR tolazoline).TI,AB. 8. (acetylcholine OR alprostadil OR amiodarone OR amlodipine OR amrinone OR amyl ADJ nitrate OR bencyclane OR bepridil

(Continued)

#13 theobromine OR theophylline OR thiouracil OR tolazoline OR trapidil OR trimetazidine OR verapamil OR xanthinol
#14 adrenomedullin OR aligeron OR ataprost OR benturodil OR briserin OR bucindolol OR carvedilol OR cicaprost OR ciclonicate OR cilostazol OR eliprodil OR fenoldopam OR ifenprodil OR imazodan
#15 lemakalim OR lemildipine OR maxadilan OR nicametate OR nipradilol OR pimobendan OR piroximone OR propentofylline OR proxazole OR proxyphylline OR tetramethylpyrazine OR timolol OR tiodazosin OR visnadine
#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 HEARING LOSS SUDDEN single term (MeSH)
#18 HEARING LOSS SENSORINEURAL explode all trees (MeSH)
#19 HEARING LOSS single term (MeSH)
#20 DEAFNESS single term (MeSH)
#21 hearing NEAR los* OR DEAF*
#22 #18 OR #19 OR #20 OR #21
#23 sudden* OR abrupt* OR rapid* OR acute*
#24 #22 AND #23
#25 SSHL OR SNHL OR ISHL OR ISSHL OR ISSNHL
#26 #17 OR #24 OR #25
#27 #16 AND #26

OR milrinone OR molsidomine OR moxisylyte OR niacin OR nicardipine OR nicergoline OR nicorandil OR nicotinyl OR nifedipine OR nimodipine OR nisoldipine OR nitrendipine
#7 nitroglycerin OR nitroprusside OR nonachlazine OR oxprenolol OR oxyfedrine OR pentaerythritol OR perhexiline OR phenoxybenzamine OR pinacidil OR pindolol OR polymethyl OR prenylamine OR propranolol OR "sodium azide" OR suloctidil OR theobromine OR theophylline OR thiouracil OR tolazoline OR trapidil OR trimetazidine OR verapamil OR xanthinol
#8 adrenomedullin OR aligeron OR ataprost OR benturodil OR briserin OR bucindolol OR carvedilol OR cicaprost OR ciclonicate OR cilostazol OR eliprodil OR fenoldopam OR ifenprodil OR imazodan
#9 lemakalim OR lemildipine OR maxadilan OR nicametate OR nipradilol OR pimobendan OR piroximone OR propentofylline OR proxazole OR proxyphylline OR tetramethylpyrazine OR timolol OR tiodazosin OR visnadine
#10 atropine OR carbogen
#11 naftidrofuryl* OR prostacyclin* OR nafronyl OR hydroxyethyl OR buflomedil* OR loftyl OR taprosten OR sadamine OR trimetazidine OR trental OR dusodril OR HES OR HAES
#12 vincamine OR vincapront OR puerarin OR anisodamine OR flunaricine OR nimodipine OR xanitol OR nicotinate OR regeneresen OR vinpocetin
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 "Hearing Loss, Sudden"[Mesh]
#15 "Hearing Loss, Sensorineural"[Mesh]
#16 "Hearing Loss"[Mesh]
#17 "Deafness"[Mesh]
#18 #15 OR #16 OR #17
#19 sudden* OR abrupt* OR rapid* OR acute*
#20 #18 AND #19

OR bradykinin OR calcitonin OR celiprolol OR chromonar OR cromakalim).TI,AB.
9. (cyclandelate OR diazoxide OR dihydroergo$8 OR dilazep OR diltiazem OR dipyridamole OR doxazosin OR dyphylline OR enoximone OR ergoloid OR erythrit$2 OR fendoldopam OR heptaminol OR hexobendine).TI,AB.
10. (iloprost OR isosorbide OR isoxsuprine OR isradipine OR kallidin OR khellin OR methylmethacrylate OR mibefradil OR milrinone).TI,AB.
11. (molsidomine OR moxisylyte OR niacin OR nicardipine OR nicergoline OR nicorandil OR nicotinyl OR nifedipine OR nimodipine OR nisoldipine OR nitrendipine OR nitroglycerin OR nitroprusside OR nonachlazine).TI,AB.
12. (oxprenolol OR oxyfedrine OR pentaerythritol OR perhexiline OR phenoxybenzamine OR pinacidil OR pindolol OR polymethyl OR prenylamine OR propranolol OR sodium ADJ azide OR suloctidil).TI,AB.
13. (theobromine OR theophylline OR thiouracil OR tolazoline OR trapidil OR trimetazidine OR verapamil OR xanthinol).TI,AB.
14. (adrenomedullin OR aligeron OR ataprost OR benturodil OR briserin OR bucindolol OR carvedilol OR cicaprost OR ciclonicate OR cilostazol OR eliprodil OR fenoldopam OR ifenprodil OR imazodan).TI,AB.
15. (lemakalim OR lemildipine OR maxadilan OR nicametate OR nipradilol OR pimobendan OR piroximone OR propentofylline OR proxazole OR proxyphylline OR tetramethylpyrazine OR timolol OR tiodazosin OR visnadine).TI,AB.
16. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. SUDDEN-DEAFNESS.DE.
18. PERCEPTION-DEAFNESS.DE. OR HEARING-LOSS.DE.
19. (hearing NEAR los$3 OR deaf$4).TI,AB. 20. 18 OR 19

(Continued)

	#21 SSHL OR SNHL OR ISHL OR ISSHL OR ISSNHL #22 #14 OR #20 OR #21 #23 #13 AND #22	21. (sudden$2 OR abrupt$2 OR rapid$2 OR acute$2).TI,AB. 22. 20 AND 21 23. (SSHL OR SNHL OR ISHL OR ISSHL OR ISSNHL).TI,AB. 24. 17 OR 22 OR 23 25. 16 AND 24

CINAHL (Datastar)	**mRCT**	
1. VASODILATOR-AGENTS#.DE. 2. (vasodilat$3 OR vasoacti$3).TI,AB. 3. (flunarizine OR betaserk OR pentoxifylli$2 OR betahistine OR nitric ADJ oxide OR prostaglandin OR lipoprostaglandin OR nylidrin OR papaverine OR nicotinic OR histamine OR atropine OR carbogen).TI,AB. 4. (nafronyl OR naftidrofuryl$15 OR prostacyclin$1 OR hydroxyethyl OR buflomedil$13 OR loftyl OR taprosten OR sadamine OR trimetazidine OR trental OR dusodril OR HES OR HAES).TI,AB. 5. (vincamine OR vincapront OR puerarin OR anisodamine OR flunaricine OR nimodipine OR xanitol OR nicotinate OR regeneresen OR vinpocetin).TI,AB. 6. (inosine OR isoprinosine OR hydralazine OR apresdine OR minoxidil OR loniten).TI,AB. 7. (fendiline OR felodipine OR adenosine OR lidoflazine OR vincamine OR tolazoline).TI,AB. 8. (acetylcholine OR alprostadil OR amiodarone OR amlodipine OR amrinone OR amyl ADJ nitrate OR bencyclane OR bepridil OR bradykinin OR calcitonin OR celiprolol OR chromonar OR cromakalim).TI,AB. 9. (cyclandelate OR diazoxide OR dihydroergo$8 OR dilazep OR diltiazem OR dipyridamole OR doxazosin OR dyphylline OR enoximone OR ergoloid OR erythrit$2 OR fendoldopam OR heptaminol OR hexobendine).TI,AB. 10.(iloprost OR isosorbide OR isoxsuprine OR isradipine OR kallidin OR khellin OR methylmethacrylate OR mibefradil OR milrinone).TI,AB. 11.(molsidomine OR moxisylyte OR niacin OR nicardipine OR nicergoline OR nicorandil OR nicotinyl OR nifedipine OR nimodipine OR nisoldipine OR nitrendipine OR nitroglycerin OR nitroprusside OR nonachlazine).TI,AB. 12.(oxprenolol OR oxyfedrine OR pentaerythritol OR perhexiline OR phenoxybenzamine OR pinacidil OR pindolol OR polymethyl OR prenylamine OR propranolol OR sodium ADJ azide OR suloctidil).TI,AB. 13.(theobromine OR theophylline OR thiouracil OR tolazoline OR trapidil OR trimetazidine OR verapamil OR xanthinol).TI,AB. 14.(adrenomedullin OR aligeron OR ataprost OR benturodil OR briserin OR bucindolol OR carvedilol OR cicaprost OR ciclonicate OR cilostazol OR eliprodil OR fenoldopam OR ifenprodil OR imazodan).TI,AB. 15.(lemakalim OR lemildipine OR maxadilan OR nicametate OR nipradilol OR pimobendan OR piroximone OR propentofylline OR proxazole OR proxyphylline OR tetramethylpyrazine OR timolol OR tiodazosin OR visnadine).TI,AB. 16.1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 17.HEARING-DISORDERS#.DE.	(sudden AND hear%) OR (sudden AND deaf%) OR SSHL OR SNHL OR ISHL OR ISSHL OR ISSNHL	—

(Continued)

18.(hearing NEAR los$3 OR deaf$4).TI,AB.
19.17 OR 18
20.(sudden$2 OR abrupt$2 OR rapid$2 OR acute$2).TI,AB.
21.19 AND 20
22.(SSHL OR SNHL OR ISHL OR ISSHL OR ISSNHL).TI,AB.
23.21 OR 22
24.16 AND 23

WHAT'S NEW

Date	Event	Description
15 February 2010	Amended	Seven studies moved from 'awaiting assessment' to the excluded studies section, following assessment of full text/translation (Ahn 2006; Dubreuil 1986; Fisch 1983; Friedrich 1991; Giger 1979; Gutman 1995; Hoffmann 1994)

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2009

Date	Event	Description
27 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Lekha Agarwal: searching, selection of studies, data extraction, drafting of the protocol/review, assistance/guidance with statistics, data analysis and data presentation.

David Pothier: selection of studies, data extraction, assistance/guidance with statistics and data analysis.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Alprostadil [therapeutic use]; Carbon Dioxide [therapeutic use]; Hearing Loss, Sensorineural [*drug therapy]; Hearing Loss, Sudden [*drug therapy]; Nafronyl [therapeutic use]; Oxygen [therapeutic use]; Randomized Controlled Trials as Topic; Vasodilator Agents [adverse effects] [*therapeutic use]

MeSH check words

Humans