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Review

Use of Vasodilators In Idiopathic Sudden Sensorineural Hearing Loss: A Systematic Review

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To compare the effect of vasodilators with that of corticosteroids in patients with idiopathic sudden sensorineural hearing loss (ISSHL). A search in PubMed, Cochrane, and Embase was conducted. Two reviewers screened the data sources to identify articles that comply with predefined inclusion criteria. Studies that compared the therapeutic effect of vasodilators with prednisone or placebo in patients with ISSHL were identified. Five articles were selected, involving a total of 611 patients. The odds ratios for perceptive hearing levels (pure tone average) post treatment varied between 0.58 and 2.18. One study demonstrated a cumulative effect (optimal hearing recovery) when vasodilators and glucocorticoids were combined (odds ratio, 1.82). Vasodilators have no beneficial effect on the treatment of ISSHL. Some evidence suggests that a combination of vasodilators with steroid treatment results in better hearing outcome than the use of corticosteroids alone.

KEYWORDS: Vasodilator agents, sensorineural hearing loss, corticosteroids

OVERVIEW

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as an acute onset (within 72 h after the onset of symptoms) of perceptive hearing impairment resulting from an unknown origin of at least 30 dB of at least three contiguous frequencies [1]. The incidence ranges between 8 and 15 new patients per 100,000 per year [2]. A consensus on the etiological factors, including vascular, viral agents, immunological, rupture of Reissner's membrane in the inner ear, and ototoxic agents, is still a subject of debate [3]. Concordantly, treatment options diverge. According to the guidelines of the American Academy of Otolaryngology (AAO), oral application of glucocorticoids is the first-line treatment option [4]. Until recently, this is the only treatment that has been proved to result in a significant high rate of hearing recovery compared with a placebo group. A vascular disturbance in the cochlear blood flow leading to hearing impairment is a widely adapted hypothesis. Therefore, vasodilators and rheological factors might have a positive influence on hearing recovery by increasing the caliber of the blood vessels and cochlear microcirculation. Variability in the use of vasodilators in patients with sudden deafness is encountered among different countries in Europe. Previous publications have shown debatable outcome of evidence regarding these rheological agents [1]. Therefore, in this systematic review, we will encompass all available evidence to critically assess all benefits and disadvantages. Moreover, it would provide an update of the literature to support the clinician in optimal patient treatment. In this study, we compared the effect of vasodilators with that of corticosteroids in patients with ISSHL.

DATA SEARCH AND METHODOLOGY

This systematic review was written using the preferred reporting items for systematic reviews from the PRISMA statement [5]. No review protocol exists for this systematic review.

Search Strategy and Selection

We conducted a systematic literature search in PubMed, Embase, and Cochrane databases. Relevant synonyms for sensorineural deafness, vasodilator, and prednisone were combined (Table 1). No filter or publication year restriction was used. The last search date was January 26, 2016. The titles and abstracts of the retrieved articles were screened (by MBS and SC) for content to meet the inclusion criteria.

Selected articles, related reviews, and meta-analyses were manually searched for additional eligible articles.

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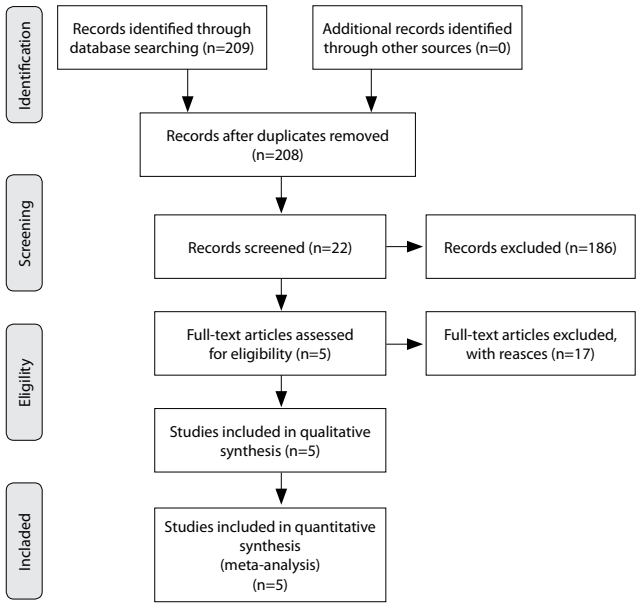

Figure 1. Flowchart

Inclusion Criteria

Inclusion criteria were patients with an acute onset (within 72 h) of hearing loss treated with vasodilators or glucocorticoids. The primary outcome measure was an improvement on audiometric evaluation [Bone Conduction pure tone average (PTA) >10 dB or Siegel's criteria I-III] after treatment. Siegel criteria I indicates complete recovery (final hearing better than 25 dB), Siegel criteria II indicates partial recovery (>15 dB gain, final hearing of 25-45 dB), Siegel criteria III indicates slight improvement (>15 dB gain, final hearing poorer than 45 dB), and Siegel criteria IV indicates no improvement (<15 dB gain, final hearing poorer than 75 dB) [6]. According to the AAO-HNS, the mean of the thresholds at frequencies 0.5, 1, 2, and 3 kHz are used to obtain the PTA [7].

Exclusion Criteria

Exclusion criteria were abstract and/or full-text not available; language other than English, Dutch, German, French, Portuguese, and Spanish; reviews or case reports; and patient group, intervention, or outcome that did not match the search criteria. Studies that compared the therapeutic effect of vasodilators with prednisone or placebo in patients with ISSHL were selected (Figure 1).

Study Assessment and Data Extraction

Predefined criteria were used for assessing the selected studies for their relevance and validity (Table 2). Relevance of the study findings for applicability depended on answering the clinical question. Therefore, four items were used: (1) evaluation of the study population, (2) the intervention, (3) the control treatment, and (4) the reported outcomes. Assessment of the validity included (1) baseline criteria, (2) standardization of intervention and control groups, (3) standardization of the outcome, (4) randomization, (5) blinding for intervention, (6) intention to treat analysis, (7) missing data, (8) handling of missing data, (9) loss to follow-up, and (10) cross-over. The studies were classified according to their level of evidence: level 1 indicating the highest and level 5 indicating the lowest level of evidence according to the Cochrane classification [8]. Outcome data of the included studies were extracted and analyzed by two independent authors (MBS and SC). For the primary outcome, odds ratios were extracted or calculated.

Table 1. Search strategy (January 2016)

Database	Search
PubMed	((((((((("hearing loss, sensorineural"[MeSH Terms]) OR hearing loss, sudden[MeSH Terms]) OR "sensorineural hearing loss" [Title/Abstract]) OR "snhl"[Title/Abstract]) OR "ssnhl"[Title/Abstract]) OR "sudden sensorineural hearing loss"[Title/Abstract]) OR "sudden deafness"[Title/Abstract])) AND (((((((vasodilator agents[MeSH Terms]) OR vasodilation[MeSH Terms]) OR vasodilat*[Title/Abstract]) OR "dilator agents"[Title/Abstract]) OR vasorelax*[Title/Abstract]) OR "vasoactive antagonists"[Title/Abstract]) OR "vasodilator agents"[Pharmacological Action])) AND ((((((((((((((((((((((prednisone[MeSH Terms]) OR prednisolon*[Title/Abstract]) OR prednison*[Title/Abstract]) OR ultracorten[Title/Abstract]) OR cortancyl[Title/Abstract]) OR decortin[Title/Abstract]) OR dacortin[Title/Abstract]) OR deltasone[Title/Abstract]) OR encorton*[Title/Abstract]) OR meticorten[Title/Abstract]) OR panasol[Title/Abstract]) OR pronisone[Title/Abstract]) OR rectodelt[Title/Abstract]) OR steroid*[Title/Abstract])))) OR "anti inflammatory agents"[Pharmacological Action]) OR "glucocorticoids"[Pharmacological Action])) OR steroids[MeSH Terms]))))
Embase	'sudden deafness'/exp OR 'sudden sensorineural hearing loss':ab,ti OR 'sudden deafness':ab,ti AND ('vasodilator agent':ab,ti OR 'vasodilatation':ab,ti OR 'vasodilator agents pharmacology':ab,ti OR 'vasodilator agents therapy':ab,ti OR 'dilator':ab,ti OR 'vasodilator agent'/exp OR 'vasodilatation'/exp) AND ('prednisone'/exp OR 'steroid'/exp OR 'predni son':ab,ti OR 'prednisolone':ta,ti OR 'steroid':ab,ti OR 'anti inflammatory agent':ab,ti OR 'glucocorticoid':ab,ti) AND [em base]/lim NOT [medline]/lim
Cochrane	prednisolon*:ti,ab or prednison*:ti,ab or ultracorten:ti,ab or cortancyl:ti,ab or decortin:ti,ab or dacortin:ti,ab or delta sone:ti,ab or encorton*:ti,ab or meticorten:ti,ab or panasol:ti,ab or pronisone:ti,ab or rectodelt:ti,ab or steroid*:ti,ab AND vasodilat*:ti,ab orm "dilator agents" ti,ab or vasorelax*ti,ab or "vasoactive antagonists" ti,ab AND "sensorineural hearing loss":ti,ab or "snhl" or "ssnhl":ti,ab or "sudden sensorineural hearing loss":ti,ab or "sudden deafness":ti,ab

OUTCOME AND ANALYSIS

Description and Assessment of Studies

A total of 209 articles were screened for title and abstract. Overall, 23 articles were found to be potentially eligible for answering the research question. Five articles were extracted and analyzed. The reference check did not result in additional articles. The relevance and validity of the included studies are demonstrated and summarized in Table 2. All retrieved studies were of moderate (level 2b) to high methodological quality (level 1) based on the international accepted standards of the Cochrane handbook [8]. Two studies were retrospective [9, 10] and three were prospective [11-13], involving a total of 611 participants. The assessment of these studies revealed no uniformity in patient inclusion regarding the onset of hearing impairment (within 48 h [7] to up to 2 weeks [8-11] after beginning of symptoms), treatment allocation (various doses depending on the chosen medication

Table 2. Critical appraisal and critical appraisal legend

	Relevance				Validity										
					Randomization										
	Patient	Intervention	Comparison	Outcome	Blinding	Intention to treat	Baseline criteria	Standardization intervention	Standardization control	Standardization outcome	Loss to follow-up	Missing data	Handling of missing data	Cross-over	Level of evidence
Fetterman et al. [9] (1996)	●	●	●	●	○	○	?	○	○	●	●	?	?	?	2b
Ogawa et al. [11] (2002)	●	◪	●	●	?	?	●	●	●	●	?	?	?	●	1b
Kanzaki et al. [12] (2003)	●	●	●	●	●	○	●	●	●	●	?	●	○	?	1b
Ahn et al. [13] (2005)	●	◪	●	●	○	?	●	●	●	●	?	?	?	●	1b
Lee et al. [10] (2012)	●	◪	●	●	○	?	●	●	●	○	?	?	?	●	2b

Legend

Relevance	Validity	Standardization outcome
Patient	Blinding	● Yes
● patients with an acute onset (within 72 h) of hearing loss	● Yes	○ No
○ patients with hearing loss (>72 h or not reported)	○ No	
	◪ Yes, but with limitations	Loss to follow-up
Intervention		● ≤10%
● treated with vasodilators	Intention to treat	○ >10%
◪ treated with vasodilators and glucocorticoids	● Yes	
	○ No	Missing data
Comparison		● ≤10%
● treated with glucocorticoids	Baseline criteria	○ >10%
◪ treated with glucocorticoids and other drugs (cocktail treatment)	● Comparable groups	
	○ Not comparable	Handling of missing data
Outcome	◪ Partially comparable	● Multiple imputation
● improvement on audiometric evaluation (Bone Conduction PTA >10 dB or Siegel's criteria I-III)	Standardization intervention	○ Excluded from analysis ◪ Single imputation
○ No improvement on audiometric evaluation	● Specified doses, duration, and administration route	
	○ Unspecified	Cross-over
	◪ Partially specified	● ≤10%
		○ >10 %
	Standardization control	
	● Specified doses, duration, and administration route	
	○ Unspecified	
	◪ Partially specified	not reported

Table 3. Effect of interventions

Study	Treatment group (n)	Control group (n)	Total (n)	Follow-up duration	Outcome (% hearing improvement) Bone conduction PTA >10 dB or Siegel's criteria I-III			
					Vasodilators	Steroids	Combination Vasodilator + steroid	Odds ratio
Fetterman et al. [9] (1996)	41	87	128	7.1 months (SD=13.7)	45.0% (18/41)	47.6% (42/87)	62.9% (63/100)	vasodilator vs steroid: 0.84 combination vs steroid: 1.82
Ogawa et al. [11] (2002)	29	28	57	1-2 months	-	75% (21/28)	75.9% (22/29)	1.05
Kanzaki et al. [12] (2003)	110	92	202	1 month	PGI2: 66.5% (23/41) PGE1: 77.4% (49/69)	BM: 75.4% (18/34) HC: 79.4% (40/58)	-	PGI2 vs BM: 1,14 PGI2 vs HC: 0.58 PGE1 vs BM: 2.18 PGE1 vs HC: 1.10 PGI2+PGE1 vs HC+BM: 1.11
Ahn et al. [13] (2005)	85	43	128	2 months	-	60.5% (26/43)	70.5% (60/85)	1.57
Lee et al. [10] (2012)	52	44	96	2 months	-	52.3% (23/44)	53.8% (28/52)	1.52

PGI2: Beraprost sodium; PGE1: Alprostadil; BM: Betamethasone; HC: Hydrocortisone; SD: standard deviation

regime), or outcome measures (two studies reported their results according to the Siegel's criteria [10,13], two studies used the criteria of the Acute Severe Hearing Loss Study Group [11, 12], and one study used a PTA of ≥10 dB [9]). Randomization and adequate blinding of the studies was either not reported or the information was lacking [11-13]. One large wellconducted multicenter study achieved reproducible baseline criteria, standardization, and randomization [12]. However, unequivocal treatment strategies were chosen (six different regimens). In the retrospective studies, selective reporting cannot be ruled out [9, 10]. Missing data were reported in all selected studies except for one [10].

Effect of Interventions

The five selected studies showed different outcomes according to their respective treatment protocol. Some showed significant improvement after treatment compared with the control group, although other studies did not reveal evidence in favor of any intervention [9-13]. Fetterman et al. [9] demonstrated that no difference exists in the outcome between steroid or vasodilator treatment; however, they found a possible cumulative effect (optimal hearing recovery) when these treatments were combined. Ogawa et al. [11] and Ahn et al. [13] found an improvement in hearing level at 4 kHz and 8 kHz, particularly in patients with severe tinnitus or vertigo. Odds ratios for perceptive hearing levels (PTA) after treatment varied between 0.58 and 2.18. These outcome data are described in Table 3. Follow-up duration varied between 1 and 7 months.

ANALYSIS AND FUTURE PERSPECTIVES

This study aimed to assess the effect of vasodilators compared with that of steroids on patients with ISSHL. Most of the studies did not compare steroids with vasodilators. In three of the five studies (Ogawa et al. [11], Ahn et al. [13], and Lee et al. [10]), both intervention and control groups used steroids. The use of steroids is generally accepted as an appropriate treatment for ISSHL [4]; therefore, it seems unethical nowadays to treat patients with vasodilators alone for research purposes. We had to exclude some articles from our literature search due to language barriers; this may have affected our findings. In 2009, Agarwal et al. [1] published a Cochrane review regarding vasodilators and vasoactive substances for ISSHL. We chose to exclude this article because two (Ni 2004 [14] and Poser 1992 [15]) out of three studies did not match our inclusion criteria. Most of the included studies were of relatively poor quality. The studies used different outcomes, three articles used a reduction in PTA of 10 dB [9, 11, 12], and two studies used an improvement of 15 dB, according to the Siegel's criteria [10, 13]. Therefore, the results of the studies that used the Siegel's (more strict) criteria may be inferior to those of studies that used 10 dB as the cut-off value. There may be an underestimation of the treatment effect applied by the latter two authors (Lee et al. [10] and Ahn et al. [13]). A 10 dB hearing improvement is not clinically relevant for the patient. Vasodilators are not to be considered useful even if 10 dB improvement is not met.

In the study by Fetterman et al. [9], 50% of the included patients had already been evaluated or treated by other physicians before presentation at their ear, nose, and throat department; this might have substantially affected the outcome. In addition, the investigators did not provide the dose and duration of the treatment but only the medication used. Unfortunately, the general characteristics of the population were calculated for the overall group and not separately for the analyzed group. This selection bias might influence the interpretation of the hearing outcomes.

Kanzaki et al. [12] used different strategies for drugs application (oral and intravascular) and some patients received treatment without hospitalization. Furthermore, compliance regarding the administered oral drugs was not verified. After the 7-day treatment, choice of medical treatment was at the discretion of each medical center [12]. Because the treatment after the termination of the trial has not been specified, it is impossible to determine the extent of contribution of the single drug therapy to the hearing outcome. The randomization in this study was not adequate; each participating center received two drugs, and each center was blinded for the type of drugs provided [12]. Moreover, it was uniquely administered to determine the effect of an individual drug. However, the methodology of blinding

has not been accurately described; thus, a lack of uniformity in drug application among centers should not be underestimated. Furthermore, the number of cases in each group (vasodilators or steroids) included in the different cooperating departments was unequal.

Another study selected patients for lipo-prostagladin (PG) E1 treatment according to their preference, without randomization or blinding [13]. Thus, full information of potential benefits and side effects of the therapeutic doses of lipo-PGE1 was offered to the patients. The provided conclusions that no significant difference was observed in age, sex, duration between the onset and diagnosis, and initial hearing level between lipo-PGE1 treatment and control groups should be critically assessed given the poor methodological quality of this study [13].

The studies fail to conclude whether vasodilators lead to a better hearing outcome than steroids. The effect of vasodilators remains unproven, although one included study in this systematic review showed some favorable outcome when applied in parallel with steroids [9]. The authors stated that further research (prospective, double-blinded with appropriate methodological basis) will be useful and necessary to further illuminate this subject area.

A strength of our review is that we conducted a broad search, limiting publication bias. Limitations were exclusion of articles without available full-text. We did not exclude studies of minor validity; this might have led to less stronger proof of evidence to support our conclusion.

CONCLUSION

The results of this review show no beneficial effect of vasodilators on the treatment of ISSHL. No significant difference was observed between the intervention and control groups in the improvement of PTA despite higher cure rate in the intervention group. Some evidence suggests that a combination of vasodilators with steroids treatment results in a better hearing outcome than the use of corticosteroids alone. Further research will be necessary to clarify this medical challenge.

Peer-review: Externally peer-reviewed.

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