The Laryngoscope

Meta-Analysis for the Effect of Medical Therapy Vs. Placebo on Recovery of Idiopathic Sudden Hearing Loss

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Objectives: To estimate the effect of recovery of idiopathic sudden hearing loss under placebo (first aim) and under medical therapy (second aim).

Study Design: Systematic review and meta-analysis.

Methods: A total of 1,674 studies published between January 1974 and April 2009 were found following suggestions in the *Cochrane Handbook for Systematic Reviews*. After filtering by criteria of Cochrane Collaboration, four trials remained for continuous and two for dichotomous data.

Results: Using Review Manager, weighted mean difference as well as standardized mean effect of hearing recovery were calculated and pooled. The values for weighted mean difference of hearing gain in dB were 0.79, 95% confidence interval (CI) (−2.04–3.61) and for standardized mean effect 0.06, 95% CI (−0.13–0.24), respectively, which computationally favors active treatment, but statistically is not significantly different from no effect (0 dB). This was in accordance to the comparison of descriptive means between recovery under placebo with 14.3 dB and active treatment with 15.8 dB hearing gain. Treatment effect of dichotomous data (hearing gain vs. no hearing gain) suggested a statistically significant better outcome for active treatment; the odds ratio (OR) [fixed] is 2.18 (1.06–4.46).

Conclusions: In five different statistical analysis methods used, treatment effect of medical therapy was slightly better than recovery under placebo in which spontaneous recovery could be assumed, but no significant effect was detected. Against the background of recovery under placebo of 14.3 dB vs. 15.8 dB hearing gain of active treatment as averages of all measured frequencies, recovery under placebo seems not to have worse outcome than recovery under medical therapy.

Key Words: Systematic review, meta-analysis, sudden hearing loss, idiopathic, sudden deafness, recovery under placebo, medical therapy, spontaneous recovery, rheological treatment.

Level of Evidence: 1a.

***Laryngoscope,* 120:1863–1871, 2010**

INTRODUCTION

Idiopathic sudden hearing loss (ISHL), also known as sudden deafness, has been defined as a mostly unilateral, sensorineural hearing dysfunction of unknown etiology and pathogenesis located in the inner ear that occurs suddenly within seconds to hours. Due to the idiopathic character of the disease, there is no generally accepted causal therapy and no approved drug in this indication.[1] Latest investigations have shown a rising incidence rate up to 160 cases in 100,000 people per year in Germany.[2,3]

Evaluation of any therapy of ISHL is complicated by the clinical observation that there is a certain rate of spontaneous improvement. Data given in the literature vary between 35%[4] and 68%.[5,6] To our knowledge, no concise accepted analysis of this spontaneous recovery rate has been published to date. Determining treatment efficacy is difficult in the absence of data from an appropriate control population. The following meta-analysis is an attempt to give verifiable and accurate data of the natural history of ISHL. As a second aim, we tried to detect the effect of any therapy used by studies with a good methodologic and clinical study design.

As part of the polypragmatic Stennert protocol,[7] rheologic treatment is a common therapy regime in Germany for ISHL and a suggested treatment of the Guideline "Sudden Deafness" of the German Society of Otorhinolaryngology–Head and Neck Surgery.[1]

Rheologic treatment has numerous biologic actions, dependent on the drug used (e.g., hydroethyl starch, dextran, pentoxifylline, prostaglandine): decreased blood

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Editor's Note: This Manuscript was accepted for publication April 15, 2010.

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DOI: 10.1002/lary.21011

viscosity by hemodilution effect, inhibition of platelet and erythrocyte aggregation, and reduced markers of inflammation and endothelial injury. In general this leads to improved microcirculation, greater capillary flow and a better oxygen supply of the cochlea.[8]

MATERIALS AND METHODS

The systematic review has been conducted according to explicit and reproducible methodology as suggested by the Cochrane Collaboration in the *Cochrane Handbook for Systematic Reviews of Interventions*,[9] containing the following steps:

- Formulation of the problem
- Searching for literature
- Evaluation of study quality
- Data collection and comparison
- Analysis and interpretation of results

Sudden hearing loss was only considered as ISHL when four requirements were met:[1]

- Sensorineural hearing impairment
- Hearing loss within minutes or hours
- Unknown origin of sudden hearing loss
- In the majority of cases unilateral

The first aim of this systematic review was to perform a meta-analysis for the spontaneous recovery of ISHL. The authors were aware that a prospective cohort study (level of evidence 1b) or randomized controlled trials (level of evidence 1b) that investigated a nontreated group of ISHL patients might not exist. For that case we assumed that recovery under placebo is supposed to be similar to spontaneous recovery under the conditions of randomized controlled trials. We did not search for low evidence level trials (e.g., case-control studies or case series) of nontreated patients.

Literature Research

For meta-analysis, several accepted sources were searched to identify primary studies from the year 1974 to April 2009. This included the Cochrane controlled clinical trials register, Silverplatter CD-ROM 1974 to 1998; Cochrane controlled clinical trials register (online) 2000 to April 2009; Medline 2000 to April 2009; EMBASE 2000 to April 2009; the Knowledge Finder 1975 to April 2009, which is mainly based on the database Medline; the Polish medical bibliography (Polska bibliographia lekarska [PBL])[10] 1979 to 2009; and other databases provided by the German national library of medicine (ZBMed).[11] "Grey literature" and personal communications were excluded. The search was conducted as recommended by Cochrane Collaboration consisting of the search terms sudden OR acute, deafness OR hearing loss, randomized OR controlled, study OR trial, therapy OR treatment, and their combinations and alterations in spelling using explicit search strategy for each source used.[9] The terms were searched for in English and with marginal variations in German and Polish language.

In addition, the MeSH terms "sudden deafness" and "sudden hearing loss" (Medline) and "nagła gluchota" (PBL) were searched for.

The literature search was conducted extensively and was designed to get a large amount of hits for trials on ISHL.Using these criteria, more than 100,000 articles were identified. After removal of duplicates and obviously different subjects than idiopathic sudden hearing loss, 1,674 publications remained for the period January 1974 to April 2009 (Table I).

TABLE I.
Search Procedure.

Step of Evaluation	No. of Trials/ References
▶ Primary search	>100,000
▶ After removal of duplicates and articles on obviously different subjects	1,674
▶ After removal of articles by methodologic restrictions (Table IIa), regardless of study design	246
▶ Trials on idiopathic sudden hearing loss	246
● retrospective	167
● prospective	79
control group	43
no control group	36
randomized + placebo-controlled + double-blind*	8
▶ After evaluation of trials by clinical criteria (Table IIb)	
continuous data	4
dichotomous data	2

*Real placebo-control (not allowed were active treatment + placebo as control group).

Among all 1,674 publications we did not find any prospective cohort study (level of evidence 1b) or randomized controlled trial (level of evidence 1b) that investigated a nontreated group of ISHL patients. Therefore, meta-analysis was realized from prospective, randomized, placebo-controlled trials (also level of evidence 1b).

In the following step we used methodologic restrictions (Table IIa) to realize a practicable meta-analysis from these placebo-controlled trials in which spontaneous recovery could be assumed. As a second aim, we performed a meta-analysis of treatment effects of medical therapy, separately for each treatment regime. After filtering by the criteria of Table IIa—regardless of study design—246 publications came into evaluation. Among them, we found 167 retrospective and 79 prospective studies. Only eight prospective studies were randomized and had a real placebo-control group consisting only of administration of placebo without any active treatment. All eight were double-blind.

After filtering by the criteria of Table IIb, four trials remained for analysis of continuous data (hearing gain in dB ± standard deviation): Desloovere et al., 1988;[14] Klemm et al., 2007;[15] Michel et al., 1991;[16] and Probst et al., 1992.[17] Two trials remained for analysis of dichotomous data (hearing gain vs. no hearing gain): Klemm et al., 2007[15] and Olszewski et al., 1990.[18]

We investigated the methodologic quality of the included trials suggested by the *Cochrane Handbook for Systematic Reviews*.[9] For this, there is no accepted gold standard and the validity of any scaling system or checklist is limited, so the results must be used with caution.[9] Therefore, we use a simple checklist that includes only major demand on study design (randomization, blinding, intention-to-treat [ITT] analysis, concealed allocation of patients, a complete reporting, and complete outcome data) as suggested by Cochrane Collaboration.

Statistical Analysis

We compared first the magnitude of recovery under placebo and second the magnitude of treatment effects of medical

TABLE IIa.
Methodologic Restrictions.

Inclusion Criteria	Exclusion Criteria
▶ Prospective, randomized, placebo-controlled trials	▶ Recrudescence ISHL
▶ Publication in English, German, or Polish	▶ Secondary treatment regimes (after failing of primary therapy)
▶ Hearing loss explicit due to ISHL	▶ Reviews, case reports
	▶ Invasive treatment (transtympanic treatment, stellate blockade, acupuncture) or inhalative treatment (HBO, carbogen inhalation)

TABLE IIb.
Clinical Criteria.

- ▶ Treatment evaluation: 7–10 days after start of therapy
- ▶ Beginning of treatment within a mean of 10 days after the event
- ▶ Outcome measures: hearing gain in dB (±standard deviation) or relative hearing gain [hearing gain/initial HL] (±standard deviation)
- ▶ Duration to treatment ≤10 days
- ▶ Homogenous treatment regime in each treatment group
- ▶ Per oral or intravenous administration

ISHL = idiopathic sudden hearing loss; HBO = hyperbaric oxygen; HL = hearing loss.

therapy using standardized mean effect and weighted mean difference of the principal outcome variable (absolute hearing gain). Therefore, the Review Manager[19] was used. Due to the small number of studies, our analysis was based on a fixed effects model, in which between-study heterogeneity is ignored. In addition, we performed an analysis using the random effect model, which generates a wider 95% confidence interval (CI) of the pooled result, and therefore generates a more conservative estimate of the effect.

TABLE III.
Characteristics—Treatment Regime of the Eight Placebo-Controlled Studies.

	Population No.			
Trial	Treatment	Control	Intervention	Control
Cinamon et al., 2001	10	11	Prednisone (1 mg/kg/day), 5 days (p.o.)	Oral placebo, 5 days (p.o.)
Desloovere et al., 1988	54	48	HAES 10% (200/0.5) 500 ml + Pentoxifyllin 15 ml, 10 days (i.v.)	NaCl 0.9% 500 ml + Placebo 15 ml, 10 days (i.v.)
Klemm et al., 2007	52 (i)	52	(i) HAES (130/0.4) 45 g/day in 750 ml isotonic NaCl, 6 days (i.v)	Glucose 5% solution 750 ml/day, 6 days (i.v.)
	53 (ii)		(ii) HAES (130/0.4) 30 g/day in 750 ml isotonic NaCl, 6 days (i.v.)	
	51 (iii)		(iii) HAES (130/0.4) 15 g/day in 750 ml isotonic NaCl, 6 days (i.v.)	
Kroneberg et al., 1992	13	14	Procain 2% in NaCl 0.9% 500 ml, 4×/week (i.v.); Dextran 40, 500 ml, 4×/week (i.v.), for max. 3 weeks	NaCl 0.9% (i.v.), 8×/week, for max. 3 weeks
Michel et al., 1991	10	11	Prostacyclin (PGI_2 - Taprosten) 25 ng/kg/minute in 2.5–3 ml NaCl 0.9% (6 hr infusion) 1× daily, 5 days (i.v.)	Mannitol 30 mg in 2.5–3 ml NaCl 0.9% (6 hr infusion) 1× daily, 5 days (i.v.)
Olszewski et al., 1990	15	15	Prostacyclin (PGI_2 - Flolan) 1.8 μg/kg (6 hr infusion) 2× daily 2 days, then 1× daily 1 day (i.v.)	Placebo (6 hr infusion) 2× daily 2 days, then 1× daily 1 day (i.v.)
Probst et al., 1992	53 (q)	67	(q) [Dextran 20 ml div] + [Dextran 40,500 ml/2 hr + Pentoxifyllin (POF) 300 mg i.v.] + [Dextran 40,500 ml/12 hr + POF 900 mg i.v.] 1 day; then Dextran 40,500 ml/4 hr i.v. + POF 300 mg i.v. + POF 2× 400 mg daily p.o. 6 days; then POF 3× 400 mg daily 27 days p.o.	[NaCl 0.9% 20 ml div] + [NaCl 0.9% 500 ml/2 hr i.v.] + [NaCl 0.9% 500 ml/12 hr i.v.] 1 day; then NaCl 0.9% 500 ml/4 hr i.v. + Placebo 2× daily p.o. 6 days; then Placebo 3× daily 27 days
	64 (qq)		(qq) [NaCl 0.9% 20 ml div] + [NaCl 0.9% 500 ml/2 hr + Pentoxifyllin (POF) 300 mg i.v.] + [NaCl 0.9% 500 ml/12 hr + POF 900 mg i.v.] 1 day; then NaCl 0.9% 500 ml/4 hr i.v. + POF 300 mg i.v. + POF 2× 400 mg daily p.o. 6 days; then POF 3× 400 mg daily 27 days p.o.	
Wilson et al., 1980	11 (y)	34 (x)	(y) Dexamethasone 0.75–4.5 mg 2× daily (p.o.); 10 days	(x) Placebo (p.o.)
	22 (yy)	52 (xx)	(yy) Methylprednisolone 4–16 mg 3× daily (p.o.); 12 days	(xx) No treatment

HAES 10% (200/0.5): hydroxyethyl starch 10% (200/0.5) (HAES-steril® 10%); HAES 130/0.4: hydroxyethyl starch 130/0.4; Pentoxifyllin (Trental®) for Desloovere et al., 1988/Pentoxifyllin for Probst et al., 1992; NaCl 0.9%: sodium chloride 0.9%; Prostacyclin (PGI_2 - Taprosten®) Grünenthal, Aachen, Germany; Prostacyclin (PGI2, Floan® f-my Wellcome, Great Britain or Chinoin, Hungary); Dextran 40: Low-molecular dextran (molecular weight of 40,000).

TABLE IV.
Characteristics—Design and Endpoints of the Eight Placebo-Controlled Studies.

Trial	Treatment	Time of Treatment Evaluation	Interval to Start of Treatment	Variable	Annotation
Cinamon et al., 2001	Oral	At 6th day	tg: 3.5 days[†] cg: 5.4 days[†]	Hearing threshold at 1st and 6th day, no SD, not clearly definable categories*	Randomized, double-blind, placebo-controlled
Desloovere et al., 1988	Parenteral	Until the 10th day	Average 7 resp. 6 days	Average absolute hearing gain in dB	Randomized, double-blind, placebo-controlled
Klemm et al., 2007	Parenteral	At 7th day	Average 2.1 days (SD: 1.9)	Average absolute hearing gain in dB	Randomized, double-blind, placebo-controlled
Kroneberg et al., 1992	Parenteral	After 24 treatments, corresponding 3 weeks*	All patients <14 days	Hearing threshold before and after therapy	Randomized, double-blind, placebo-controlled; not explicitly prospective
Michel et al., 1991	Parenteral	At 8th day	All patients <8 days	Hearing threshold at 1st and 8th day	Randomized, double-blind, placebo-controlled
Olszewski et al., 1990	Parenteral	At 3rd day	All patients <7 days	Categories[‡]	Randomized, double-blind, placebo-controlled
Probst et al., 1992	Oral + parenteral	8 to 10 days after beginning of therapy	Average 2 days, always <14 days	Averaged absolute hearing gain in dB	Randomized, double-blind, placebo-controlled
Wilson et al., 1980	Oral	4 weeks and 3 months after beginning of therapy*	All patients <10 days	Categories	Placebo-controlled, double-blind; not explicitly prospective, randomization unclear*

*Lead to rejection for final analysis.
[†]Average.
[‡]Only analysis of dichotomous data possible.
tg = treatment group; cg = control group; SD = standard deviation.

To compare the effect of medical treatment with the latest meta-analyses on ISHL,[20–24] which compared dichotomous data (hearing gain vs. no hearing gain) of randomized controlled trials, we also performed an analysis of those data, if possible. The best possible analysis was conducted out of two adequate trials, which gave information about hearing gain in categories.[15,18] The odds ratio (OR) and 95% CI were estimated for each study. The Q-test was performed to assess heterogeneity and, if not significant ($P > .05$), ORs were pooled according to the fixed effect model. In addition, we also performed an analysis using the random effect model.

RESULTS

The baseline characteristics of the included trials such as study population, frequencies measured for pure-tone average, age, gender, initial hearing loss (HL) are comparable throughout the trials to a large extent (Tables III, IV, V).

Unexpectedly, all included trials treated the patients of the investigation group with a rheologic therapy regime (Table III).

So an analysis of treatment effect—our second aim—in this setting is an analysis of rheologic treatment and is therefore not shown additionally. Values of outcome are shown in Figure 1. Studies that investigated other treatment regimes than rheologic therapy (steroids, antiviral therapy, etc.) did not fulfill the demanded criteria (Table IIa,b).

The absolute hearing gain in dB with standard deviation was calculated[14] from the original data given by the article or by personal communication.[16,17] The data are listed in Table V and are given as averages calculated over all measured frequencies.

The weighted mean difference and standardized mean effect were calculated and pooled for continuous data (hearing gain in dB). The respective values are 0.06, 95% CI (−0.13–0.24) for standardized mean effect and 0.79 (−2.04–3.61) for weighted mean difference of hearing gain. This was in good accordance with the simple comparison of descriptive means of hearing gain between active treatment 15.8 dB and recovery under placebo with 14.3 dB. The analysis did not give any

TABLE V.
Outcome of Included Trials.

Trial	Frequencies Measured [kHz]	Initial HL [dB]		Hearing Gain [dB]		Statistical Evaluation by the Author of the Trial
		Treatment	Control	Treatment	Control	
Desloovere et al., 1988	0.5/1/2/4	41 (±26)	40 (±24)	15.2 (±22.8)	10.7 (±19.4)	No significant difference found between groups.
Klemm et al., 2007	4 Frequencies out of (0.5/1/2/3/4)	41 (±18)		(i) 15.5 (±13.6) (ii) 16.9 (±13.4) (iii) 18.3 (±13.9) (all) 16.9 (±13.6)	15.5 (±13.6)	Statistically significant ($P < 0.05$) greater rate of recovery for patients with (a) duration to treatment >2 days and/or (b) RR systolic >140 mmHg treated with HAES than with Placebo.
Michel et al., 1991	0.125/0.25/0.5/1/2/4/8	46.8 (±23.5)	30.9 (±14.7)	20.6 (±15.4)	20.8 (±14.3)	No significant difference found between groups.
Olszewski et al., 1990	0.5–4	Hearing loss and hearing gain only given in categories				Statistically significant ($P < 0.05$) greater rate of complete recovery for patients treated with PGI2 (86%) than with placebo (7%).
Probst et al., 1992	0.5/1/2/4/6/8	(q) 49 (±28) (qq) 52 (±26)	54 (±26)	(q) + (qq) 14.1 (±13.5)	15.0 (±15.8)	No significant difference found between groups.

Values are shown as means ± standard deviation.
(All) value for tg1 + tg2 + tg3.
HL = hearing loss.

evidence for a statistically significant effect in favor of active treatment and for placebo. The data are presented in exploratory forest plots (Fig. 1a–d).

The included trials showed a high level of methodologic quality (Table VI), even though four studies did not report about allocation concealment[14,16–18] and three trials did not report about intention-to-treat analysis.[14,17,18]

In addition, by using the given dichotomous data (hearing gain vs. no hearing gain), the OR (fixed effect model) was 2.18 (1.06–4.46) and the OR (random effect model) was 2.36 (0.84–6.65). This suggests a statistically significant effect for rheologic treatment against placebo. The rheologic therapy regime (see also Table III) consisted either of hydroxyethyl starch [HES 130/0.4][15] or of prostacyclin [PGI_2].[18] However, this result must be viewed with caution. First, the I^2 analysis shows variability of 29.1% for this analysis, and the OR (random effect model) shows only a trend toward the active treatment but did not give evidence for a statistical significant effect. Second, there is no uniform definition, neither in our nor in the other meta-analyses of the term "hearing gain" in the analysis of dichotomous data, so the comparison of those data is limited. Third, in order to realize a meta-analysis from these dichotomous data we had to stretch the criterion of Table IIb "time of treatment evaluation 7–10 days after start of therapy" into "*<10 days after start of therapy.*" The data are presented in exploratory forest plots Fig. 2a and Fig. 2b.

DISCUSSION

The number of scientific articles published about the therapy of ISHL has grown so large around the world that the data are confusing.[1,8] Even a large amount of reviews could not solve the problem.[20–26] Most studies and reviews dealing with the topic of ISHL treatment are faced with the problem that there is a lack of evidence about the natural history of ISHL. Therefore, major uncertainties and differing opinions have led to a plethora of controversial therapy strategies, thus confusing health care organizations, law courts, insurance companies, patients, and doctors.

Particularly the discussion about the natural history of ISHL has reached a level where the question to treat or not to treat arises. Mattox and Simmons[5] were the first to examine the spontaneous recovery. In former East-Germany, Weinaug et al.[6] counted the spontaneous remission rate up to 68%. Our group found in a placebo-controlled study a rate of 65%, when treated within the first week and normal hearing before the event.[16,27] Nevertheless, concise reviews for the natural history are missing at the present state.

Heiden et al.[28] calculated by arithmetical mean the spontaneous improvement by reviewing publications of Mattox et al.,[5] Laird et al.,[29] Weinaug et al.,[6] and Wilson et al.[4] up to 50%, but the authors were aware that their work lacks statistical clearness and reproducibility.

Our meta-analysis summarizes the hearing gain methodologically between the placebo and active treatment groups of the individual studies, the so-called

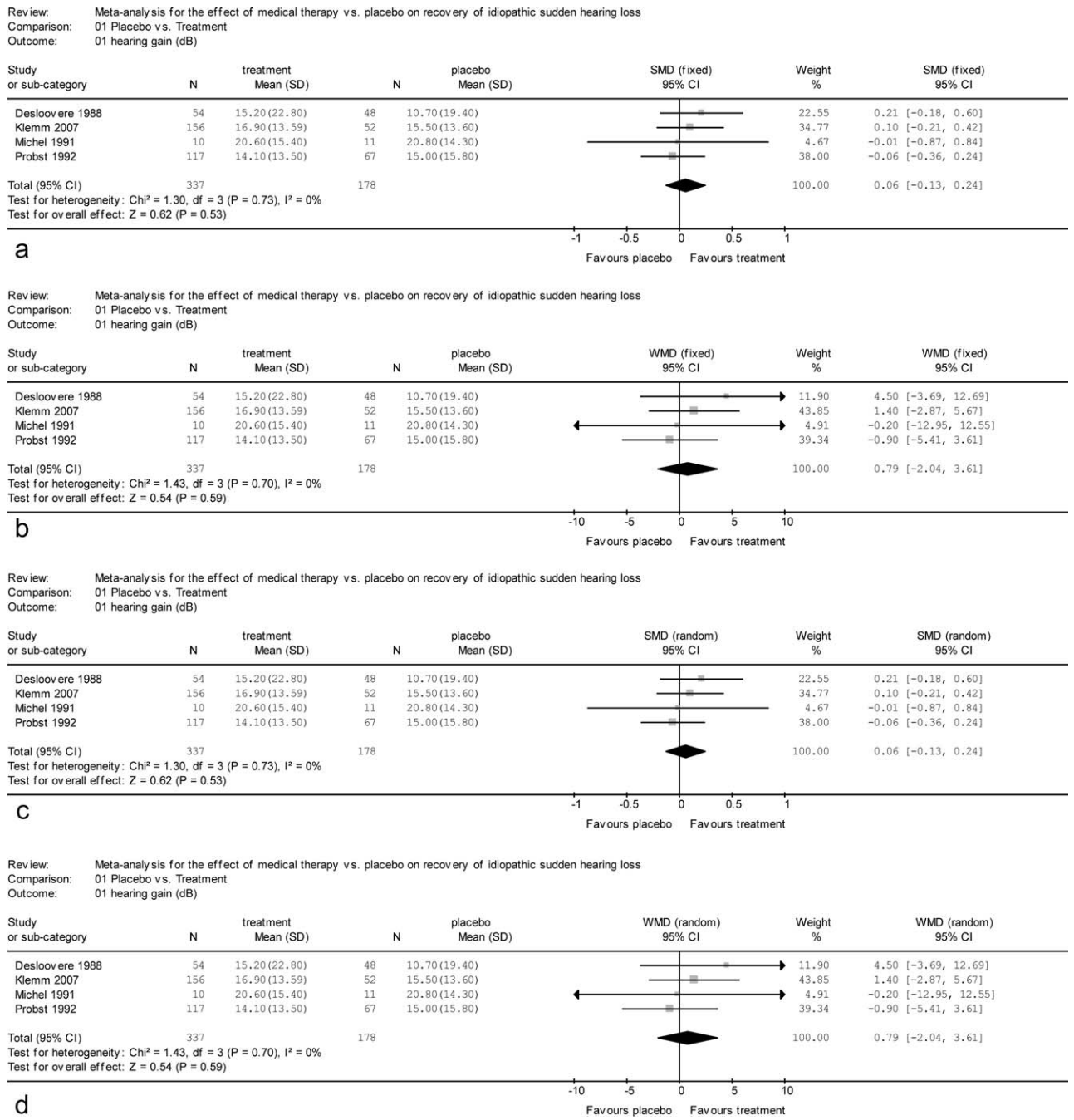

Fig. 1. Meta-analysis for the effect of medical therapy vs. placebo on recovery of idiopathic sudden hearing loss (ISHL) (continuous data). (a) Standardized mean effect, fixed effect model. (b) Weighted mean difference, fixed effect model. (c) Standardized mean effect, random effect model. (d) Weighted mean difference, random effect model. SD = standard deviation; 95% CI = 95% confidence interval; SMD = standard mean effect; WMD = weighted mean difference; fixed = fixed effect model; random = random effect model.

"standardized effect-difference." This must not inevitably follow the original scale (like decibel, "dB"), but can also be done on a relative scale to compensate study intern inherent distortions.

The rationale behind this approach is the attempt to balance the different measuring methods and conditions of the diverse studies under the assumption that within the studies the same settings for the measurement of both placebo and active treatment patients existed.

Therefore, the main idea of a meta-analysis is to pool the differences of the effects between placebo and active treatment, which were seen within the studies, in order to quantify the common effect over all included studies.

We only included randomized, placebo-controlled, double-blind trials for meta-analysis. Under these conditions, recovery under placebo is supposed to be similar to the effect of no treatment, in other words

TABLE VI.
Methodologic Quality of Included Trials.

	Desloovere, 1988	Klemm, 2007	Michel, 1991	Olszewski, 1990	Probst, 1992
▶ Adequate randomization	+	+	+*	(+)	(+)
▶ Intention-to-treat analysis (ITT)	[–]	+	+*	[–]	[–]
▶ Adequate blinding (single- or double-blind)	+	+	(+)	(+)	+
▶ Aside from the experimental treatment, patients were treated equally	+	+	+	+	+
▶ Allocation of patients was concealed	[–]	+	[–]	[–]	[–]
▶ No selective reporting	+	+	+	+	+
▶ Complete outcome data	+	+	+	+	+
▶ Free of other bias	+	+	–	–	+
Σ (Quality scale)	6/8	8/8	6/8	5/8	6/8

( ) Reported but no detailed explanation.
[ ] Not reported and therefore inadequate.
*Extra information by author of trial.

"spontaneous recovery." Randomized, placebo-controlled trials seem to be the best available evidence for the natural history of ISHL, even though the effect is only similar to spontaneous recovery and not spontaneous recovery itself.

For the first aim of our analysis, we could not detect any clinically relevant and statistically sound difference in the effect of treated vs. placebo groups in which a spontaneous recovery could be assumed. The hearing gain within the reported 95% confidence intervals for the difference never showed a clinically relevant cut away from zero.

The hearing gain within the reported period was calculated as 14.3 dB for recovery under placebo and as 15.8 dB for treated groups, ignoring adjustment for patient number and variance.

The pooled difference of 0.79 dB computationally favors active treatment but statistically is not significantly different from no effect (0 dB). Accordingly, recovery under placebo seems not to have worse outcome than recovery under medical therapy.

Analysis of the effect of rheologic treatment—our second aim—did not differ from the first analysis because all included trials investigated rheologic

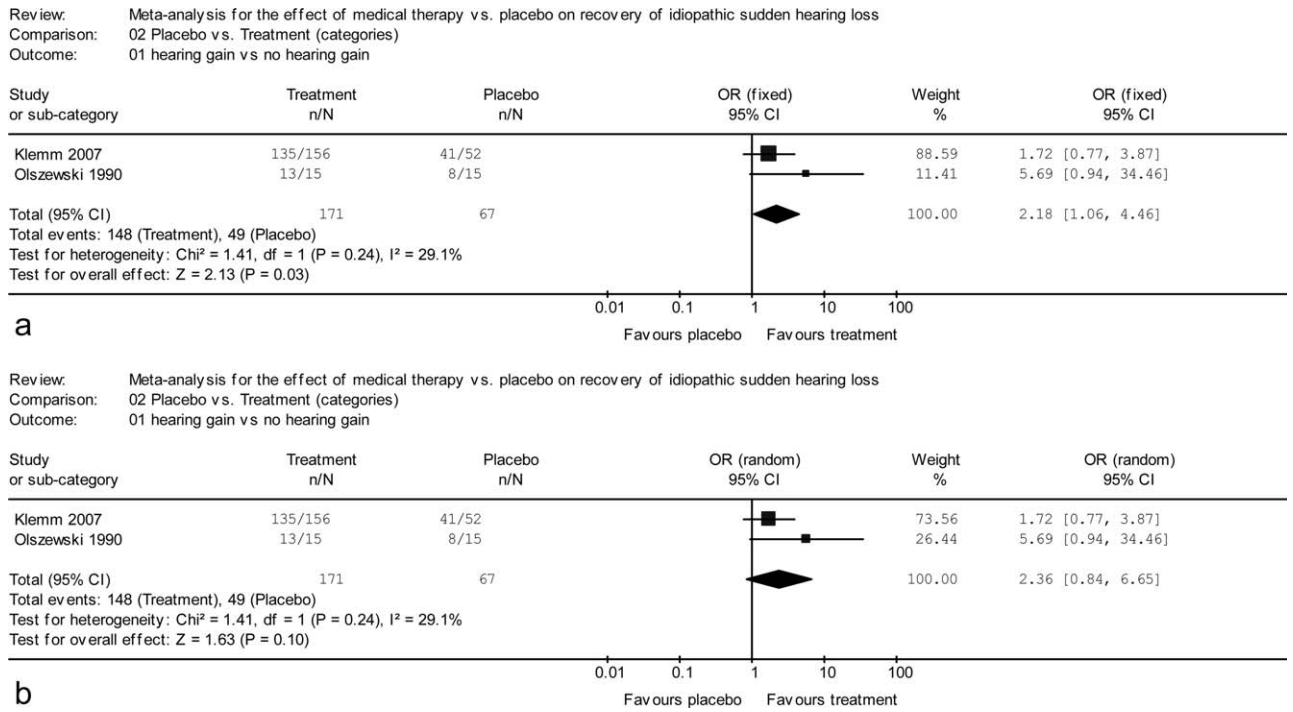

Fig. 2. Meta-analysis for the effect of medical therapy vs. placebo on recovery of idiopathic sudden hearing loss (ISHL) (dichotomous data). (a) Odds ratio, fixed effect model. (b) Odds ratio, random effect model. SD = standard deviation; 95% CI = 95% confidence interval; OR = odds ratio; fixed = fixed effect model; random = random effect model.

therapy. Rheologic treatment seems not to have an impact on hearing improvement, looking only at the analysis of continuous data.

By analyzing the dichotomous data for the effect of rheologic treatment, we found an OR (fixed effect model) of 2.18 (1.06–4.46), which suggests a statistically significant better outcome of hearing recovery for rheologic treatment compared with placebo. To our knowledge, it is the first comprehensible analysis of comparable trials on ISHL that suggests a significant effect for a treatment against placebo. However, this result must be viewed with caution because of the great amount of variability ($I^2 = 29.1\%$) and the varying definition of "hearing gain."

Varying results of analyzing continuous data and dichotomous data may have different reasons.

First, the odds ratios are a weaker statistical measure than weighted mean differences.

Second, the outcome measurement may have influence on the analysis outcome. A retrospective analysis and review of literature by Plontke et al.[30] showed a lack of agreement for different outcome measures, more for pure-tone average (continuous data) than for dichotomous data (hearing gain vs. no hearing gain). Although the study had a retrospective study design, it gives a clue for the challenging analysis of those trials. Other authors[15] state that the calculation of hearing gain as average overall measure frequencies may lead to a dilution of treatment effect and suggest alternative assessment of hearing recovery (calculation of hearing gain out of the affected frequencies). In addition, "floor effects" (ceiling effects) can prevent detection of a significant difference[31] in continuous data.

One of the major problems of comparing ISHL trials was the heterogeneity of the definition of hearing loss, measured frequencies, calculation of pure-tone average, initial hearing loss, time to start of treatment, time of treatment evaluation, and outcome measurement throughout the different studies. Comparison of trials and ignoring these differences may lead to biased analyses. Time until the start of treatment[6,8,32] and time of treatment evaluation[8] may have an impact on the measured hearing gain. Moreover, the hearing gain varies between patients with first-time ISHL and recrudescence ISHL. Furthermore, patients with secondary treatment regimes after failing of primary therapy cannot be compared with first-line treatment patients.

What was striking was the fact that among the 1,674 published studies only four (for continuous data) and two (for dichotomous data) trials met the criteria given by the Cochrane Collaboration[9] and could be evaluated. Any available study for ISHL should follow these rules.

CONCLUSIONS

Hearing gain was slightly better for active treatment compared with the placebo treatment in which a spontaneous recovery could be assumed but statistically not significant in five different statistical analysis methods. Recovery under placebo—14.3 dB hearing gain—as average of all measured frequencies seems not to have worse outcome than recovery under medical therapy—15.8 dB hearing gain. Only comparison of dichotomous data showed a statistically significant effect for rheologic therapy, but this result must be viewed with caution.

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