Objective: To identify, evaluate, and review randomized controlled trials (RCTs) on the treatment of sudden sensorineural hearing loss (SSHL).

Data Sources: A MEDLINE search and hand search were conducted to identify RCTs published between January 1966 and February 2006 in the English language on the treatment of SSHL. Search terms included hearing loss, sensorineural (MeSH term), sensorineural hearing loss (text words), and sudden deafness (text words).

Study Selection: Prospective RCTs on the treatment of patients diagnosed as having SSHL.

Data Extraction: One independent observer extracted study data. Validity was evaluated using standard criteria. Characteristics and results were reviewed systematically.

Data Synthesis: A total of 21 RCTs were identified regarding various treatments, including systemic and intratympanic steroids; antiviral and hemodilution agents; mineral, vitamin, and herbal preparations; batroxobin; carbogen; and hyperbaric oxygen. All studies used audiometric outcome measures. Only 2 studies used identical criteria to define SSHL. The method of randomization was described in 2 studies. Validity scores ranged from 2 to 8 (of 9). Positive results were reported favoring systemic steroids, intratympanic steroids, batroxobin, magnesium, vitamin E, and hyperbaric oxygen, although there were serious limitations in each study with a positive finding. There was no difference in audiometric outcomes reported across all studies of antiviral and hemodilution agents and no difference in one study of systemic steroids vs placebo.

Conclusions: To our knowledge, no valid RCT exists to determine effective treatment of SSHL. Systemic steroids cannot be considered the gold standard of treatment of SSHL, given the severe limitations of the landmark study supporting their use.

Arch Otolaryngol Head Neck Surg. 2007;133:573-581
IDENTIFICATION AND INCLUSION OF RCTS

A MEDLINE literature search was conducted to identify RCTs on the treatment of SSHL published in the English language between January 1966 and February 2006. The following MEDLINE search terms were used: hearing loss, sensorineural (medical subject heading [MeSH]), sensorineural hearing loss (text words), and sudden deafness (text words). Limiting search terms were therapy and clinical trials. Additional RCTs were identified by hand searching the references of original articles and review articles.

After each citation was identified through the literature search, a single reviewer (A.E.C.) independently examined the abstracts to determine suitability for inclusion. To be included in the review, each study had to be identified as a prospective RCT published in the English language and comparing a control group and a treatment group of patients with a diagnosis of “sudden sensorineural hearing loss,” “idio-pathic sudden sensorineural hearing loss,” or “sudden deafness.” Studies were not excluded on the basis of the qualitative or quantitative definitions of SSHL, treatment regimens, or outcome measures.

The initial MEDLINE search using the MeSH term hearing loss, sensorineural yielded 35 citations, of which 20 failed to meet the inclusion criteria and 18 were not published in the English language. The remaining 13 studies were included in the review. The text word MEDLINE searches and the hand search yielded 3 additional studies that were not identified through the MeSH term search, bringing the total number of articles meeting the inclusion criteria to 20.

EVALUATION OF METHODOLOGICAL QUALITY

Methodological quality was evaluated independently by one reviewer (A.E.C.) to determine the validity of each study. The reviewer was not blinded to the authors, institutions, journals of publication, or results of the studies, consistent with the Berlin method.12 The following validity criteria for assessing the study results were adapted from the Users’ Guides to the Medical Literature series, which was published by the American Medical Association and are described elsewhere.13

Primary guides
Was the assignment of patients to treatments randomized?
Was follow-up complete for at least 85% of the patients who entered the study?
Were patient analyzed in groups to which they were randomized?

Secondary guides
Were the patients blind to treatment?
Were the clinicians blind to treatment?
Were the study personnel blind to treatment?
Were the groups similar at the start of the trial?
Aside from experimental intervention, were the groups treated equally?

Additional criterion
Was the allocation of patients to treatment groups concealed?

DATA EXTRACTION

Data were extracted from included trials by one reviewer (A.E.C.). Information on the patients, investigations, methods, interventions, and outcomes were recorded on a standard-
ized data collection form. The primary outcome measure was the pure-tone average (PTA) scores. Additional outcome measures of interest included objective measures, such as speech reception thresholds and speech discrimination scores, and subjective measures, such as patient reports of tinnitus, vertigo, and perceived hearing improvement. Authors were contacted for missing information and unpublished data, although none provided additional data.

DATA SYNTHESIS

Characteristics and results of all included studies were reviewed systematically. Study characteristics, including sample populations, inclusion criteria, treatment and control therapies, and validity scores, were tabulated and compared across all 20 RCTs. Studies were then categorized by treatment protocol (Table 1). Outcome measures and results of each study were summarized and tabulated.

RESULTS

CHARACTERISTICS OF INCLUDED STUDIES

Twenty RCTs, reporting on a total of 21 treatment comparisons, met the inclusion criteria of this review. The validity scores of each trial are listed in Table 2. The mean validity score was 6.1 of 9, with a range of 2 to 8. Two of the studies described use of computer random number generators for randomization.4,28 The method of one study was pseudorandomized,16 with patients assigned to 1 of 4 treatment groups on a rotating basis. One study made no mention of randomization in its methods at all.15 The remaining 16 studies were described as randomized, but the method of randomization was not reported.

The characteristics of the included studies are summarized in Table 3. Among the 8 steroid therapy RCTs, only 215,17 specified inclusion criteria of a definition of SSHL consistent with the NICDC definition, and 2 did not provide a quantitative definition of subjects' hearing loss at all.21,22 Among the other 12 RCTs evaluating other therapies, definitions of SSHL varied considerably, and none were consistent with the NICDC definition.

INTERVENTIONS AND OUTCOME MEASURES

Table 4 summarize the outcome measures of each study. Objective outcome measures, subjective outcome measures, and scales and questionnaires were reported in the included studies. Among objective measures, PTA was reported in all 20 RCTs. Also, speech discrimination scores were reported in 6 studies,16,17,20,26,27,30 speech reception thresholds were reported in 4 studies,20,24,26,30 and otoacoustic emissions were reported in 1 study.31 Subjective outcome measures that included tinnitus were reported in 7 studies5,15,18,21,28; that included vertigo, 5 studies5,18,21,28; that included subjective hearing recovery, 5 studies5,18,19,21,28; that included sensation of increased ear pressure, 3 studies18,20,28; and that included headache, nausea, and fatigue, 1 study.31 Finally, 1 study also reported the results of the Hearing Screening Inventory and the Short Form-12 Questionnaire.17

STEROID THERAPY VS PLACEBO THERAPY

Two prospective clinical studies investigated oral steroids vs oral placebo for treatment of SSHL.15,16 Wilson et al.15 treated 33 patients with varied doses of dexamethasone (range, 0.75 mg twice daily to 4.5 mg twice daily) or methylprednisolone (range, 4 mg/d to 16 mg 3 times daily) and reported that the anti-inflammatory effect of each dose seemed roughly equivalent. Pure-tone average was measured at 4 weeks and 3 months after onset of hearing loss. Results were categorized into “recovery” and “no recovery” groups. No recovery was defined as less than 50% recovery of hearing, comparing PTA results at 4 weeks and 3 months. They found a statistically significant greater rate of recovery for patients treated with steroids (61%) compared with placebo (32%), measured at an undefined time.15

Cinamon and colleagues16 administered prednisone, 1 mg/kg daily, to 11 treatment subjects and measured PTA, speech frequency, high-tone hearing levels, and discrimination scores at 6 days (soon after treatment) and 14 to 90 days (follow-up) after treatment. Patients were categorized into “improvement” and “no improvement” groups with respect to average hearing level (increase of hearing level >15 dB), average speech frequency, and average high-tone hearing level; however, categorical improvement of discrimination scores was not reported. They reported no significant differences between steroids and placebo on all outcome measures.16

ANTIVIRAL PLUS STEROID THERAPY VS PLACEBO PLUS STEROID THERAPY

Four studies evaluated treatment of SSHL with antiviral therapy and steroid therapy vs placebo and steroid therapy. None of the studies reported statistically significant results.17,20

Tucci and colleagues17 administered valacyclovir, 1 g 3 times daily for 10 days, and tapering doses of prednisone (80-20 mg/d) for 12 days, to 39 patients. Twenty-nine control patients received the same course of prednisone plus placebo. Pure-tone average and speech discrimination scores were measured at 2 weeks and 6 weeks after treatment. Data were reported on a subset of patients who had normal hearing in the unaffected ear, but complete data on all patients included in the study were not reported. Recovery rates to within 10 dB of the nonaffected ear, 20 dB of the nonaffected ear, and to within 50% of baseline were reported. No differences between treatment groups were found.17

Westerlaken et al.18 treated 37 patients with acyclovir, 10 mg/kg 3 times daily for 7 days, and tapering doses of prednisolone (maximum dose, 1 mg/kg) for 7 days. Thirty-three control group patients were treated with prednisolone alone. Outcomes measured at 12 months after treatment included PTA, as well as subjective presence of pressure, vertigo, and tinnitus. Patients with any lesser degree of hearing loss at 12 months after treatment compared with baseline were considered to have shown “recovery.” There were no statistically significant differences reported.

Stockroos and colleagues19 applied the same acyclovir and prednisolone treatment protocols as Westerlaken et al.18 and compared 22 patients treated with acyclovir
and prednisolone with 21 patients treated with prednisolone only. An improvement in mean PTA was reported; however, standard deviation was not reported. There were no differences between the 2 treatment groups. Uri and colleagues20 treated 29 patients with acyclovir, 15 mg/kg per day, and hydrocortisone, 100 mg 3 times daily for 7 days, plus a tapering dose of hydrocortisone for an additional 7 days. They also administered hydro-
cortisone only to 31 control group patients. Pure-tone average, speech reception threshold, speech discrimination scores, stapedial reflex, tympanometry, and tone decay were measured at 1, 3, and 12 months after treatment. Uri et al20 provided graphic representation of the data; however, they did not report individual patient results, means, or standard deviations. The authors reported no significant differences.20

STEROIDS VS OTHER THERAPY

To determine whether steroid treatment might constitute the gold standard in the treatment of SSHL, all studies that compared steroid therapy with any other active treatment were reviewed. Two studies were identified. Active treatments of carbogen inhalation16 and fibrinolysis21 were compared with treatment with steroids alone.

Cinamon and colleagues5 treated 10 patients with carbogen inhalation (5% carbon dioxide and 95% oxygen) for 30 minutes 6 times per day for 5 days and another 11 patients with prednisone, 1 mg/kg daily for 5 days. Reported outcome measures were improvement in average hearing level (>15 dB), speech frequency, and high-tone hearing level soon after treatment (6 days) and at follow-up (average, 33 days). They found no significant differences between treatment with carbogen vs treatment with steroids.16

Kubo and colleagues21 devised 2 treatment groups: 82 patients received a total of 80 U of intravenous batroxobin over 13 days plus oral placebo, while 80 patients in a second treatment arm received a combination of intravenous and oral betamethasone plus placebo intravenously over 13 days.21 The number of patients with improved PTA at 2 weeks after treatment was reported. Patients were categorized as full recovery, good improvement, fair improvement, or no improvement. Kubo et al21 reported a positive study in favor of batroxobin; however, when the data are interpreted using a definition similar to definition of improvement in the study by Cinamon et al,16 there was no difference between batroxobin and steroids.

INTRATYMpanic STEROIDS FOR SALVAGE THERAPY

Ho and colleagues22 randomized patients in whom a 10-day course of conservative treatment with methylprednisolone, nicametate, vitamin B, fludiazepam, and carbogen had failed with 2 treatment groups: intratympanic dexamethasone (1 mg/mL weekly for 3 weeks) vs continuation with nicametate, vitamin B, and fludiazepam. Patients were categorized as complete, marked, slight, or no recovery on the basis of PTA at 1 and 4 weeks after treatment. A significantly greater number of patients had improvement of at least 30 dB in hearing in the intratympanic dexamethasone group (53.3%) vs the control group (7.1%) (P<.05); however, the length of time after treatment at which this effect was measured was not reported.

VASOACTIVE AND HEMODILUTION THERAPIES

Four RCTs assessed the utility of vasoactive and hemodilution treatments, including pentoxifylline, dextran, Ginkgo biloba, and nifedipine, and combinations...
### Table 4. Summary of Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroid Therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson et al.,19 1980</td>
<td>PTA at 4 and 12 wk after treatment</td>
<td>Statistically significant (P &lt; .03) greater rate of recovery for patients treated with steroids (61%) than with placebo (22%), measured at an undefined time after treatment</td>
</tr>
<tr>
<td>Cinamon et al.,20 2001</td>
<td>PTA and discrimination scores at 6 d after treatment and follow-up (average, 33 d)</td>
<td>No significant differences between any of the treatment groups (P &gt; .05)</td>
</tr>
<tr>
<td>Nageris et al.,21 2004</td>
<td>PTA and speech discrimination scores before and at 1, 3, and 12 mo</td>
<td>For audiograms, there was significantly better improvement (P &lt; .05) with defibrinogenation therapy (57.3%) than with steroids (38.7%). There was also greater improvement in tinnitus and aural fullness with defibrinogenation, and greater improvement in fatigue with steroids (P &lt; .05)</td>
</tr>
<tr>
<td><strong>Magnesium vs Other Therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordin et al.,22 2002</td>
<td>PTA, recovery rate, speech reception threshold, and speech discrimination were assessed before and after 1 wk of treatment</td>
<td>Recovery rate significantly greater (P &lt; .01) among patients treated with magnesium and carbogen (66.4%) vs patients treated with carbogen alone (49.9%).</td>
</tr>
<tr>
<td>Nageris et al.,23 2004</td>
<td>PTA and speech discrimination scores before treatment and after treatment at an unspecified time</td>
<td>Statistically greater rate of hearing improvement (at least 10 dB) in the magnesium group than in the control group (P &lt; .05)</td>
</tr>
<tr>
<td><strong>Other Therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joachims et al.,24 2003</td>
<td>PTA, recovery rate, speech reception thresholds, and speech discrimination score were assessed at an undefined time after treatment</td>
<td>The improvement rate (defined as &gt;75%) was significantly greater (P = .04) in the vitamin E group (78.8%) than in the standard group (45.5%). No significant difference in degree of recovery observed between groups</td>
</tr>
<tr>
<td>Ogava et al.,25 2002</td>
<td>PTA and tinnitus were evaluated at 1 and 2 mo after treatment</td>
<td>No significant differences found between treatment groups regarding PTA or tinnitus</td>
</tr>
<tr>
<td>Suckfüll,26 2002</td>
<td>Primary outcome measure was PTA; secondary outcome measures were hearing recovery, improvement in speech perception at 6 wk, tinnitus, and frequency of adverse effects</td>
<td>No significant differences (P &gt; .05) noted between apheresis and standard treatment groups for PTA or mean speech perception</td>
</tr>
<tr>
<td>Mora et al.,27 2003</td>
<td>PTA and otoacoustic emission tests were performed 30 d after treatment</td>
<td>No between-group comparisons reported</td>
</tr>
<tr>
<td>Topuz et al.,28 2004</td>
<td>PTA was measured before and 4 wk after treatment</td>
<td>Statistically significant greater hearing gains in the hyperbaric oxygen group than in the control group in 4 of 5 frequencies</td>
</tr>
</tbody>
</table>

Abbreviation: PTA, pure-tone average.
MAGNESIUM VS OTHER THERAPY

Two RCTs evaluated patients treated with magnesium in addition to standard therapy vs those treated without magnesium. Gordin and colleagues \(^\text{26} \) reported a significantly greater recovery rate among patients treated with magnesium and carbogen (n=73) vs patients treated with carbogen alone (n=60); however, with a poor validity score of 2 of 9, the applicability of the results is questionable. Nageris et al \(^\text{31} \) reported a significantly greater rate of recovery among patients treated with steroids plus magnesium (n=14) vs steroids plus placebo (n=14) as measured by PTA 4 weeks after treatment. However, they did not specify what steroid was given or the length of treatment.

OTHER THERAPIES

Five RCTs assessed the utility of other treatment protocols, and only 2 reported statistically significant results. Joachims and colleagues \(^\text{27} \) compared patients who were treated with vitamin E in addition to standard treatment (steroids, carbogen, and magnesium) vs standard treatment alone. They found no difference in degree of recovery with the addition of vitamin E when PTAs were categorized as full, good, moderate, or no recovery; however, a quantitative definition, in decibels, of these categories of improvement was not provided. They did, however, find a statistically significant greater rate of recovery, defined mathematically as the hearing gain after treatment divided by the difference in initial hearing level between the affected and unaffected ear, multiplied by 100.

Topuz and colleagues \(^\text{32} \) compared 34 patients receiving hyperbaric oxygen plus standard treatment (prednisone, Rheomacrodex [dextran 40; Medisan Pharmaceuticals, Uppsala, Sweden], diazepam, and pentoxifylline) vs 21 patients receiving standard treatment alone. They found a greater rate of improvement, defined as gain of hearing of at least 10 dB on PTA, in the hyperbaric oxygen group. However, the time after treatment at which this was measured was not reported.

The remainder of the 3 RCTs, studying fibrinogen, recombinant tissue plasminogen activator, and prostaglandin \(\text{E}_2\), did not report positive results (see Table 3 [other therapies] and Table 4 [other therapies] for further details).

In the landmark study by Wilson and colleagues \(^\text{15} \), treatment with steroids resulted in a statistically significant greater rate of recovery than oral placebo. Multiple reviews have hailed this study as the best evidence for the treatment of SSHL. However, the methodological validity of this study is significantly limited. First, while the study by Wilson et al \(^\text{15} \) has been labeled an RCT in multiple other reviews of SSHL, the inclusion trial itself was never described as such. Nowhere in the article is the study described as a randomized study. Its inclusion in this systematic review is only on the basis of it being cited in other review articles. By methodological criteria (Schultz et al \(^\text{33} \)), the study by Wilson et al \(^\text{15} \) is not an RCT. The consequences of nonrandomization are well known, with consistent evidence that nonrandomized studies produce exaggerated treatment effects. Therefore, one cannot be certain that the positive treatment effect reported by Wilson et al \(^\text{15} \) after treating patients with SSHL with oral steroids can be considered a valid one.

Second, additional methodological characteristics of the study by Wilson et al \(^\text{15} \) make it difficult for the clinician to know how to treat a patient with SSHL with steroids and what outcomes to expect. The doses of steroids used in the study by Wilson et al \(^\text{15} \) varied considerably across the patients; this was reconciled with the statement that the antiinflammatory effect of the varied doses of steroids was thought to be “roughly equivalent.” Also, the time at which the outcome was measured was not specified. The study therefore does not inform the otolaryngologist of what dose of steroids to use, nor at what time after treatment to expect improvement.

By contrast, a pseudorandomized controlled trial of 20 patients with SSHL \(^\text{28} \) found no statistically significant difference between treatment with steroids and oral placebo. Certainly, the sample size in this study was small, but it is nonetheless interesting that, with the addition of some degree of randomization, the positive treatment effect attributed to oral steroids was not reproduced.

The present systematic review also allows additional conclusions to be drawn regarding therapies that are ineffective. Four RCTs demonstrated no evidence for an added benefit with the addition of antiviral therapy to steroid therapy. Also, no RCT on vasoactive and hemodilution substances, such as pentoxifylline, dextran, \(G. \text{biloba}\), or nifedipine, found positive results. As independent variables, fibrinogen and low-density lipoprotein apheresis, prostaglandin \(\text{E}_1\), and recombinant tissue plasminogen activator \(^\text{31} \) had no benefit in the treatment of SSHL.

This systematic review also identified several RCTs with positive results. Batroxobin, a snake venom with defibrinogenation properties, was found to give positive audiometric results compared with betamethasone; however, the inclusion criteria of this were not clearly specified, and therefore one cannot be certain that the subjects had a diagnosis of SSHL consistent with the NICDC definition. \(^\text{25} \) The addition of magnesium sulfate to carbogen treatment yielded positive audiometric results; however, with a validity score of 2 of 9, the results of this study must be interpreted with caution. \(^\text{26} \) The addition of magnesium to steroid treatment also resulted in greater PTAs, yet the duration of treatment was not reported. \(^\text{27} \) Vita-
min E appears to add benefit to standard treatment of patients with SSHL, but again, the duration of therapy required to obtain this effect was not reported. Hyperbaric oxygen may also provide better PTAs after treatment, but the study reporting this finding was of limited methodological quality (3 of 9 criteria). Finally, positive results were found among patients treated with intratympanic dexamethasone after treatment with steroids and carbogen had failed, although the definition of SSHL was not quantitatively defined in this study.

This systematic review has limitations that should be considered when interpreting the results. First, only articles published in the English language were included in the review. The English-language bias is notable to the extent that there are known regional differences in the treatment of SSHL. The consequence is that many RCTs on the treatment of SSHL with vasoactive and hemodilution substances were excluded. However, Reissner and Weidauer state that, in Germany, where many hemodilution therapies are used for the treatment of SSHL, "the preference for a particular therapy can scarcely be based on the results of scientific studies." Moreover, hemodilution therapies have been rejected in many North American centers because of potentially fatal adverse effects. The clinical significance of this limitation, therefore, is questionable.

This systematic review is also inherently limited by the RCTs on which it is based. First, the definition of SSHL varied widely across the 20 studies, with only 2 studies having definitions of SSHL that matched the NICDC definition precisely. This presents considerable limitations for the otolaryngologist, who must try to decide if the results of the studies apply to a given patient with SSHL. Second, many different outcomes were measured at many different times after treatment, again limiting the validity of between-study comparisons and generalizability to the population of patients with SSHL. Finally, the overall validity scores of the studies were marginal, with no study meeting all 9 validity criteria.

There are, however, important strengths of this review. Previous reviews have been criticized for lack of a rigorous, systematic approach. This review engages a rigorous and scientific approach, while providing transparency of the literature search, methodological validity scores, and summary of the included studies. Also, to our knowledge, it is the largest systematic review of RCTs on SSHL.

Traditionally, SSHL has been treated in North America with systemic steroids, yet the evidence for this is questionable. Positive results have been reported in RCTs conducted outside of North America using a variety of treatment protocols, including batroxobin, magnesium, vitamin E, and hyperbaric oxygen. Interestingly, intratympanic steroid injections have also been shown to produce statistically significant greater rates of recovery among patients in whom an initial 10-day course of treatment with systemic steroids, carbogen, nicametate, and vitamin B had failed. However, none of these studies was without limitations, and future research is needed to further evaluate the positive findings reported in this study. In the meantime, it is imperative that universally accepted, quantitative definitions of SSHL and the clinical outcomes by which to measure it are developed to aid the otolaryngologist in applying research findings to the clinical setting.

Submitted for Publication: August 8, 2006; final revision received November 1, 2006; accepted January 24, 2007.

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Author Contributions: Drs Conlin and Parnes had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Conlin and Parnes. Acquisition of data: Conlin. Analysis and interpretation of data: Conlin and Parnes. Drafting of the manuscript: Conlin and Parnes. Critical revision of the manuscript for important intellectual content: Conlin and Parnes. Statistical analysis: Conlin. Administrative, technical, and material support: Conlin. Study supervision: Parnes.

Financial Disclosure: None reported.

Previous Presentation: This study was presented at the Canadian Meeting of Otolaryngology Head and Neck Surgery 59th Annual Meeting; June 22, 2005; St John’s, Newfoundland.


