Chinese herbal medicine for idiopathic sudden sensorineural hearing loss: a systematic review of randomised clinical trials

Su, C.-X.,[1,2] Yan, L.-J.,[2] Lewith, G.[3] & Liu, J.-P.[1]

[1]*Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China,* [2]*School of Nursing, Beijing University of Chinese Medicine, Beijing, China, and* [3]*Center for Research on Complementary and Alternative Medicine, University of Southampton, Primary Care, Southampton, UK*

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Background: Idiopathic sudden sensorineural hearing loss has great impact on quality of life. Many clinical trials using Chinese herbal medicine for idiopathic sudden sensorineural hearing loss have been conducted and reported beneficial results. However, there is no critical appraised evidence on efficacy and safety of Chinese herbal medicine for idiopathic sudden sensorineural hearing loss to inform clinical use.
Objective of review: To assess the beneficial effect and safety of Chinese herbal medicine for idiopathic sudden sensorineural hearing loss.
Type of review: Systematic review of randomised clinical trials.
Search strategy: Seven electronic databases and two trial registries were searched for all eligible trials from inception to January 2013.
Evaluation method: Two authors independently selected trials and extracted data. The Cochrane risk of bias tool was utilised to assess the methodological quality of the included trials. REVMAN 5.2 software was applied for data analysis with effect estimate presented as risk ratio and mean difference with its 95% confidence interval.
Results: Forty-one randomised clinical trials involving 3560 participants were identified. Five kinds of Chinese herbal medicine were trialed. All trials compared conventional therapies of steroids, vasodilaltors, anticoagulants, nutritional supplements or hyperbaric oxygen with or without herbal medicine. No trial was identified that compared herbal medicine alone with placebo. No trial was identified that blinded the participants or the observers to their herbal medication. Only one trial adequately reported its method of randomisation. No trial reported the sample size calculated to show an effect. All trials had material other defects giving a high likelihood of bias. Because of the overall poor quality of all 41 trials, it was concluded that there was no level-one evidence to support the use of Chinese herbal medicine, alone or in addition to conventional therapies, to improve the hearing in adults with idiopathic sudden sensorineural hearing loss. Two trials reported adverse effects, and no severe adverse effects were found in the Chinese herbal medicine groups.
Conclusions: The existing evidence for the beneficial effect and safety of Chinese herbal medicine for idiopathic sudden sensorineural hearing loss comes from methodologically poor studies and therefore cannot be reliably used to support their clinical use. We identify a justification to further investigate the effect and safety of Chinese herbal medicine for people with idiopathic sudden sensorineural hearing loss in rigorously designed randomised trials.

Background

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as an abrupt or rapidly progressing hearing loss of at least 30 decibels in at least three contiguous audiometric frequencies over 72 h or less without recognised cause despite adequate investigation.[1] The incidence of ISSHL is reported as ≈8–15 per 100 000 persons per year,[2,3] with some estimates ranging as high as 160 per 100 000 per year.[4] The cause of ISSHL remains unclear. There may be different mechanisms, such as vascular disturbance, viral infection, autoimmune disease or an inner ear membrane rupture.[5,6]

ISSHL has a significant impact on people's conversation and hearing in nosy environments. Their inability to localise sound may be very dangerous and put people at risk.[1] Quality of life in people with ISSHL is diminished, and sufferers are more likely to experience anxiety and depression.[7,8] Tinnitus and dizziness associated with ISSHL also diminish quality of life.[9]

Correspondence: J.-P. Liu, Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, 11 Bei San Huan Dong Lu, Chaoyang District, Beijing 100029, China. Tel.: +86 10 64286760; Fax: +86 10 64286871; e-mails: Liujp@bucm.edu.cn; or jianping_l@hotmail.com

Treatments for ISSHL have been diverse owing to its unknown aetiology.[1] The most widely used therapeutic agents focus on improving oxygenation of the inner ear and blood circulation, involving corticosteroids, vasodilator agents, anticoagulants, volume expanders, hyperbaric oxygen and antivirals.[1,10] However, there is no proven evidence to support clinical benefit of these therapies.[11–15]

Chinese herbal medicine (CHM) is widely used in China and other East Asian countries. ISSHL was first identified in Yellow Emperor's Inner Canon in the warring states period (475-221BC).[16] According to traditional Chinese medicine theory, ISSHL is caused by wind-cold, wind-heat, hyperactivity of liver-fire, *yin* deficiency and *yang* excess, *qi* stagnation and blood stasis, stagnation of phlegm-fire.[17] Clinical treatment using CHM is based on the principle of dispelling these pathogenic processes and normalising the body's balance.[17]

Many clinical studies of CHM for ISSHL have been conducted and reported with some promising results.[18–24] However, there is no systematic summary of current evidence on efficacy and safety of CHM for ISSHL to justify their clinical use. The objectives of this review are to assess the effect and safety of CHM for ISSHL.

Methods

Registration number

The protocol of this systematic review has been registered in PROSPERO (available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013003515).

Eligibility criteria

We included randomised clinical trials which reported the effect of CHM for ISSHL with no limitation on language, blinding or publication type. ISSHL must be diagnosed with a clear description of diagnostic criteria. CHM was defined as single herb, Chinese patent medicine, practitioner-prescribed herbal formula and herbal products extracted from natural herbs regardless of dosage, administration regimen or duration. The control could be no treatment, placebo or conventional therapy. Combination of CHM with conventional therapy *versus* the same conventional therapy was also included. Quasi-randomised trials were excluded. The primary outcome was pure-tone audiometric threshold change at the end of treatment or follow-up. The secondary outcomes were improvement in hearing speech frequencies; improvement in clinical concomitant symptoms including tinnitus, dizziness, depression or anxiety; quality of life measured by a validated instrument or tool; and adverse effects associated with CHM.

Study identification and selection

We conducted systematic searches for randomised clinical trials which could be published, unpublished and ongoing. The Cochrane Central Register of Controlled Trials, PubMed, EMBASE, Chinese National Knowledge Infrastructure Databases, Chinese Science and Technology Periodical Database, Chinese Biomedical Literature Database and Wan Fang Database were searched from inception to January 2013. Ongoing registered clinical trials were searched through International Clinical Trial Registry Platform portal (http://www.who.int/ictrp/en/) and Clinical Trial Registry (http://clinicaltrials.gov/).

The following search terms were used individually or combined: 'hearing loss, sudden', 'hearing loss, sensorineural, sudden', 'sshl', 'snhl', 'ishl', 'isshl', 'issnhl', 'ssnhl', 'Chinese traditional', 'Chinese herbal', 'oriental traditional', 'herb', 'herbal medicine', 'clinical trial', and 'controlled trial'. We also checked the reference lists of eligible articles obtained for additional studies. The different strategies for the above databases are shown in Table S1.

Two authors (Su CX, Yan LJ) selected the eligible studies independently. Obviously irrelevant reports were removed after examining titles and abstracts. Full texts were retrieved if they met the eligibility criteria.

Data extraction

Two authors (Su CX and Yan LJ) independently extracted data from the included trials using a piloted, standard data extraction form. For each of the trials, the data extracted included publication year, study type, diagnostic criteria, random sequence generation, allocation concealment, blinding, sample size (total number and numbers in each group), participant characteristics, intervention and control, outcomes, conclusions, funding. For dichotomous outcomes, we extracted the number of participants with the event of interest, the number randomised to each group and the number analysed for each trial. Where study findings were uncertain or missing, we contacted trial authors for clarification and details. We resolved any differences in opinion through discussion or consultation to the third party (Liu JP).

Assessment of risk of bias

We independently assessed the risk of bias of the included studies according to the criteria from the Cochrane Handbook version 5.1.0 that included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.[25]

Quality of each trial was categorised into low/unclear/high risk of bias. If necessary, we contacted the authors of assessed trials for clarification. We resolved any differences in opinion through discussion or consultation to the third party (Liu JP).

Data analysis

REVMAN 5.2 software was used for data analyses. We performed the following comparisons if data available: CHM *versus* no treatment, CHM *versus* placebo, CHM with or without conventional therapy *versus* conventional therapy. Meta-analysis was used if the trials had an acceptable homogeneity on study design, participants, interventions, control and outcome measures. We used a fixed-effect model for the meta-analysis for non-significant heterogeneity and random-effect model for significant heterogeneity ($P < 0.1$). The effect estimate was presented as risk ratio with its 95% confidence interval for dichotomous outcome, and as mean difference with its 95% confidence interval for continuous outcome. If we had identified a sufficient number of randomised clinical trials, sensitivity analyses were performed to explore the influence of trial quality on effect estimates. Publication bias was explored using a funnel plot analysis if sufficient trials (e.g., 10 trials or over) were found.

Results

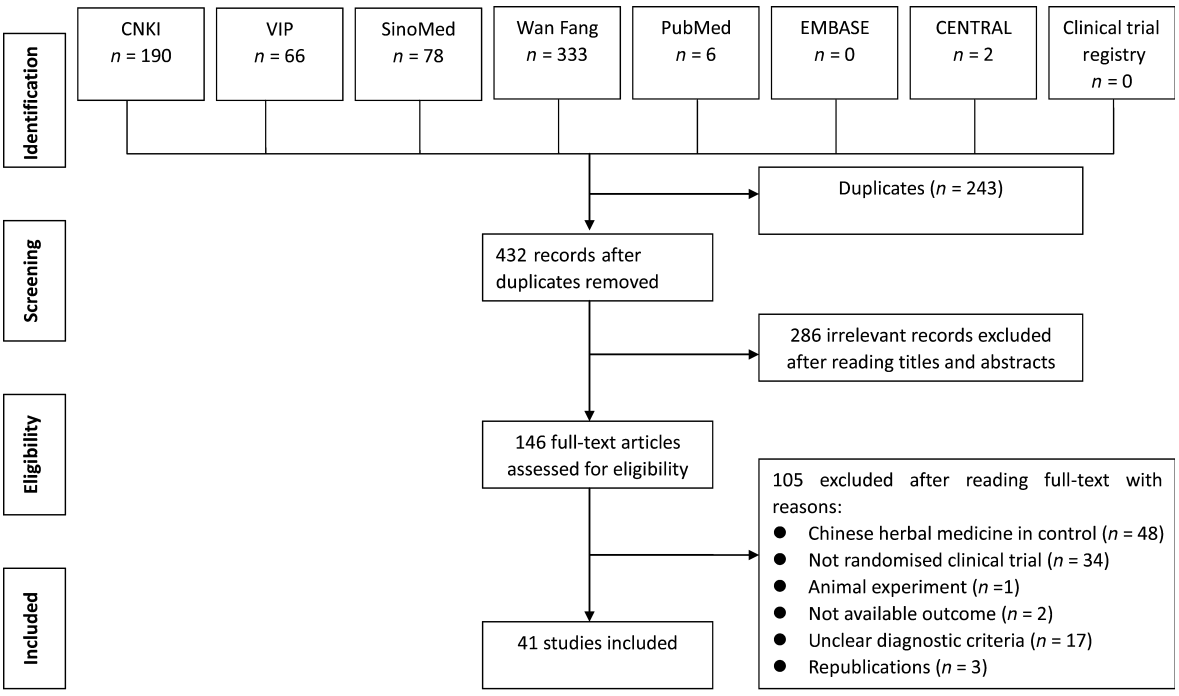
Study selection

Of 675 potential articles of interest identified from the initial search, 243 duplicates and 286 irrelevant studies were excluded by screening the titles and abstracts. Of 146 full-text articles were further checked. Finally, 41 studies met the eligibility criteria and were included in this systematic review (Fig. 1).[26–66]

Study characteristics

All trials were conducted and published in China, of which 36 were journal articles (87.8%) and five were postgraduate theses (12.2%). There were 38 trials with two arms and three trials with three arms.

Forty-one trials involved 3560 participants, ranging from 48 to 226 with an average of 86.8 per trial.[6,29] 52.8% participants were male except two trials which failed to report gender. All of the trials used Chinese national diagnostic criteria of ISSHL. Of 14 trials defining inclusion criteria, one trial only included participants 15 days after hearing loss[38] and another trial only accepted participants who were untreated 14 days before the trial.[59] There was no information on exclusion criteria in 15 trials.



Abbreviation: CNKI: Chinese National Knowledge Infrastructure Databases; VIP: Chinese Science and Technology Periodical Database; SioMed: Chinese Biomedical Literature Database; CENTRAL: The Cochrane Central Register of Controlled Trials

Fig. 1. Flow chart of study selection.

Five kinds of CHM were employed in the included trials. The formulations included herbal formula (fixed herbal formula and practitioner-prescribed herbal formula in 34 trials), powder (seven trials), herbal extract injection (six trials), pill (six trials) and capsule (one trial). No trial described quality standards of the herbal preparations. Conventional therapies included oral and injected corticosteroids, vasodilator agents, anticoagulants, a mixture of nutritional supplements and hyperbaric oxygen. The duration of treatment ranged from 7 days to 56 days.

All trials described some form of hearing assessment as the outcome. Forty-one trials reported proportions of participants with improvement in pure-tone audiometric threshold (i.e. pure-tone audiometric threshold change ≥15 dB),[67,68] and three trials also reported mean improvement in pure-tone audiometric threshold. Twelve trials reported proportion of participants with improvement in dizziness (i.e. marked relief or disappearance of dizziness)[67,68] after treatment and six trials reported proportion of participants with improvement of tinnitus (i.e. marked relief or disappearance of tinnitus) after treatment.[67,68] Only one trial reported depression and anxiety.[61] No trial reported any data on improvement in hearing speech frequencies or quality of life. Only two trials reported adverse effects.[51,62]

The characteristics of included trials are listed in Table 1.

Risk of bias

We attempted to contact with authors of all included trials for clarification and details. As few trial reports provided the contact details such as corresponding authors' phone number or email address, only one author was contactable and provided the missing information.[48]

Only one trial reported method of randomisation using 'drawing of lots'.[48] Allocation concealment was reported in only one trial as use of open random allocation schedule.[48] No trial conducted blinding. Only two trials provided details of study attrition, of which one reported no participants dropped out,[48] the other reported two participants withdrew due to some reasons, but intention-to-treat analysis was not performed.[62] To assess selective reporting, we searched the registration information of the included trials through trial registries. Unfortunately, no trial was registered and no protocol was available. Therefore, selective reporting was assessed by comparing the outcomes in the method and in the results, and five trials were considered as high risk of bias because not all the pre-specified outcomes in the method of trial publications were reported in the results.[28,40,51,61,62] No trial conducted estimation of sample size. Baseline comparability was stated in 13 trials. Consequently, all of the trials had a high risk of bias and were assessed as low quality of trials (Fig. 2).

Effect estimates

Among the 41 included trials, 35 trials addressed outcomes with exact time points, but no trial reported what the trial's primary or secondary outcome would be. No trial compared CHM to no treatment or placebo, only one trial compared CHM to conventional therapy,[40] and 40 trials compared CHM in combination with conventional therapy to the same conventional therapy. The possibility of pooling the effect estimation was limited due to issues of heterogeneity. The effect estimates of CHM are shown in the Table 2.

Mean improvement of pure-tone audiometric threshold. Of three trials providing data on this outcome at the end of treatment, only one trial demonstrated CHM was superior to conventional therapy (mean difference −26.17, 95% confidence interval −29.15 to −23.19) after 56 days treatment.[61] In contrast, data from the other trials showed no significance between groups.

Proportion of participants with improvement of pure-tone audiometric threshold. Of 41 trials reporting this outcome, only one trial tested the effect of CHM (Tongqiao Conger decoction) compared with conventional therapy (betahistine mesylate) and found no statistical difference after follow-up of 6 months (risk ratio 1.08, 95% confidence interval 0.88 to 1.32).[40] The remaining 40 trials compared CHM in combination with conventional therapy to the same conventional therapy; 50% showed significant differences favouring CHM at the end of treatment.

Proportion of participants with improvement of tinnitus and dizziness. Twelve trials provided data on improvement in tinnitus. Only six trials showed CHM led to an increase in the proportion attaining improvement in tinnitus.

Six trials reported improvement in dizziness as an outcome. One trial demonstrated CHM was superior to conventional therapy (risk ratio 8.07, 95% confidence interval 1.21 to 53.58) after 14-day treatment,[28] but conventional therapy was significantly more effective than CHM in another trial (risk ratio 0.33, 95% confidence interval 0.13 to 0.81) after 14-day treatment.[62] The remaining trials failed to find any difference.[35,36,38,51]

Improvement of depression and anxiety. Only one trial contributed result to this outcome and demonstrated statistically improvement in anxiety (risk ratio −2.80, 95% confidence interval −4.80 to −0.80) and no difference in

Table 1. Basic characteristic of included studies

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Men (%)	Intervention	Control	Outcomes
Chen[26]	ISSHL patients 1997 version	I:45(21–69) C:42(17–67)	117	65.8	Modified Man Jinzi powder or Modified Longdan Xiegan decoction or Modified Tongqiao Huoxue decoction or Modified Erlong Zuoci pill or Modified Yiqi Conger decoction according to different syndromes, one dose each time, orally, once daily plus the same conventional therapy for 14 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, anisodamine	PTATC, symptoms, adverse effects
Cui[27]	ISSHL patients 1997 version	I:16–64 C:15–63	60	51.7	Practitioner-prescribed Zishen Yangxin Huayu decoction, one dose each time, orally, once daily plus the same conventional therapy for 14 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, anisodamine, citicoline, ahylysantinfarctase	PTATC, symptoms
Duan[28]	ISSHL outpatients 1997 version	I:NR C:NR	76	52.6	Erlong 2 powder, 9 g each time, orally, twice daily plus the same conventional therapy for 14 days	Lipo PGE, vitamin	PTATC, symptoms
Guan[29]	ISSHL inpatients and outpatients 1997 version	I: 32 ± 5.21(21–57) C1: 30 ± 3.15(20–55) C_2: 29 ± 4.41(22–57)	226	55.8	Practitioner-prescribed herbal formula, one dose each time (250 mL), orally, once daily plus the same conventional therapy for 10 days	C_1:Lipo PGE, ATP, vitamin C_2:Lipo PGE, ATP, vitamin, methylprednisolone	PTATC, symptoms
Li[30]	ISSHL patients 2005 version	I: 40(25–68) C:40(25–65)	65	58.5	Practitioner-prescribed herbal formula, one dose divided into twice daily, orally plus the same conventional therapy for 9–15 days	Betahistine, dexamethasone, hydrochloride injection, flunarizine, vitamin, HBO	PTATC
Liang[31]	ISSHL patients 1997 version	I:15–63 C:14–64	60	53.3	Practitioner-prescribed herbal formula, one dose each time, orally, once daily plus the same conventional therapy for 28 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, citicoline	PTATC, symptoms

Table 1. continued

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Men (%)	Intervention	Control	Outcomes
Liang[32]	ISSHL patients 1997 version	I:NR C:NR	100	49.0	Practitioner-prescribed herbal formula, orally, plus the same conventional therapy	Low molecular weight dextran, ATP, co-enzyme A, nimodipine, DXM	PTATC
Liu[33]	ISSHL patients 1997 version	I:42(12–68) C:40.5(9–63)	60	56.7	Practitioner-prescribed herbal formula, one dose daily, orally, plus the same conventional therapy for 28 days	Low molecular weight dextran, citicoline, co-enzyme A, vitamin, fluorine gonadorelin	PTATC, symptoms
Liu[34]	ISSHL inpatients and outpatients 1997 version	I:55.7(45–70) C:53.5	68	50.0	Yishen Zhilong powder, one dose divided into twice daily (100 mL each time), orally, plus the same conventional therapy for 10 days	Low molecular weight dextran, ATP, co-enzyme A,	PTATC
Liu[35]	ISSHL inpatients 2005 version	I:19–65 C:18–62	92	54.4	Longdan Xiegan decoction, one dose divided into twice daily (200 mL daily), orally plus the same conventional therapy for 20 days	ATP, co-enzyme A, vitamin, DXM	PTATC, symptoms
Luo[36]	ISSHL patients 1997 version	I:43.5(16–75) C:45.6(18–76)	188	46.3	Practitioner-prescribed herbal formula, orally, plus the same conventional therapy for 14 days	Lipo PGE	PTATC, symptoms
Pan[37]	ISSHL patients 2005 version	I:45(21–69) C:42(17–67)	154	47.4	Xuesaitong injection, 400 mg each time, once daily plus the same conventional therapy for 10–20 days Ginkgo-damole injection, 15 mL each time, once daily plus the same conventional therapy for 10–20 days	Co-enzyme A, citicoline, vitamin, DXM, batroxobin, HBO	PTATC
Shao[38]	ISSHL outpatients 2005 version	I:46.65(21–68) C:46.87(20–68)	80	53.8	Tongqiao Huoxue powder, 205 g daily, orally plus the same conventional therapy	Lipo PGE, vitamin	PTATC, symptoms

Table 1. continued

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Men (%)	Intervention	Control	Outcomes
Shi[39]	ISSHL patients 1997 version	I:NR C:NR	80	65.0	Modified Xiaoyao powder or Modified Longdan Xiegan decoction or Modified Banxia Baizhu Tianma decoction or Modified Erlong Zuoci pill or Modified Yiqi Conger decoction plus the same conventional therapy for 28 days	ATP, co-enzyme A, vitamin, lidocaine	PTATC
Si[40]	ISSHL outpatients 2005 version	I:NR C:NR	60	51.7	Tongqiao Conger decoction	Betahistine mesylate	PTATC
Sun[41]	ISSHL patients Practical otorhinolaryngology criteria	I:15–69 C:14–71	106	45.3	Mixed Chinese herbs (practitioner-prescribed herbal formula, one dose divided into twice daily, orally, Fufang Danshen injection), 100 mL daily plus the same conventional therapy for 15 days	Betahistine sodium chloride injection, prednisolone tablet	PTATC
Sun[42]	ISSHL inpatients 1997 version	I:42.6(16–71) C:37.8(21–66)	66	62.1	Mixed Chinese herbs (Tongqiao Huoxue decoction, Xuanfei Tongqiao decoction) plus the same conventional therapy for 21 days	Corticosteroid	PTATC, symptoms
Wang[43]	ISSHL inpatients 1997 version	I:NR C:NR	50	NR	Xingqi Tongqiao Huoxue decoction, one dose divided into twice daily, orally plus the same conventional therapy	Low molecular weight dextran, ATP, co-enzyme A, vitamin, citicoline, Lipo PGE	PTATC
Wang[44]	ISSHL patients 2005 version	I:37.5(17–60) C:37.2(15–61)	50	48.0	Mixed Chinese herbs (Longdan Xiegan decoction, one dose divided into twice daily, musk external application, once 2 days) plus the same conventional therapy for 14 days	Low molecular weight dextran, batroxobin flunarizine hydrochlorid, eduxil	PTATC

Table 1. continued

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Men (%)	Intervention	Control	Outcomes
Wei[45]	ISSHL inpatients and outpatients 1997 version	I:NR C:NR	72	56.9	Practitioner-prescribed herbal formula, one dose daily, orally plus the same conventional therapy for 14 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, nicholin	PTATC
Wu[46]	ISSHL outpatients Otorhinolaryngology criteria	I:37.5(12–60) C:37.1(12–60)	60	55.0	Mixed Chinese herbs (Modified Tongqiao Huoxue decoction, one dose divided into twice daily, orally, Xuesaitong injection, 600 mg each time, once daily) plus the same conventional therapy for 14 days	DXM, vitamin, ATP	PTATC
Yang[47]	ISSHL outpatients. 1997 version	I:51(20–75) C:52(20–70)	60	60.0	Shugan Tongqiao decoction, one dose divided into twice daily plus the same conventional therapy	Fluorine gonadorelin, duxil	PTATC
Yang[48]	ISSHL patients. 1997 version	I: 40.18 ± 13.32 (19–65) C: 41.21 ± 12.07 (21–65)	120	46.7	Longdan Xiegan pill or Yinqiao powder or Erchen decoction or Erlong Zuoci pill or Buzhong Yiqi decoction according to different syndromes plus the same conventional therapy for 14 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, ahylysantinfarctase	PTATC
Yin[49]	ISSHL patients. 2005 version	I:51.6(17–83) C:47.8(17–79)	145	46.2	Practitioner-prescribed herbal formula plus the same conventional therapy for 10 days	Lipo PGE, DXM, HBO	PTATC
Yu[50]	ISSHL inpatients and outpatients 1997 version	I:41(25–70) C:40.5(23–72)	72	62.5	Practitioner-prescribed Conger decoction, one dose daily, orally plus the same conventional therapy for 14–28 days	Low molecular weight dextran, ATP, coenzyme A, vitamin,	PTATC, symptoms

Table 1. continued

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Men (%)	Intervention	Control	Outcomes
Yu[51]	ISSHL outpatients. 1997 version	I: 38.1 ± 5.0(20–69) C:38.0 ± 6.5(19–70)	65	46.2	Tuqiao Tonglong decoction orally plus the same conventional therapy for 14–28 days	Low molecular weight dextran, ATP, co-enzyme A,	PTATC, symptoms
Yuan[52]	ISSHL patients. 1997 version	I:50.5(31–70) C:51.5(35–68)	100	56.0	Kangnaoshuai capsule, six capsules each time, orally, three times daily plus the same conventional therapy for 15 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, moroxydine hydrochloride	PTATC
Zhang[53]	ISSHL patients Otolaryngology encyclopedia	I:17–64 C:16–67	78	59.0	Practitioner-prescribed herbal formula, one dose divided into twice daily, orally plus the same conventional therapy	Low molecular weight dextran, ATP, co-enzyme A, vitamin,	PTATC
Zhang[54]	ISSHL patients 1997 version	I:NR C:NR	120	61.7	Practitioner-prescribed herbal formula, one dose daily, orally plus the same conventional therapy for 14 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, HBO, DXM	PTATC
Zhang[55]	ISSHL patients 1997 version	I: 44.7(21–59) C:45.1(22–60)	48	45.8	Mixed Chinese herbs (Xuesaitong injection, 8 mL daily, Modified Longdan Xiegan decoction or Modified Qingqi Huatan pill or Modified Tongqiao Huoxue decoction or Modified Erlong Zuoci pill according to different syndromes) plus the same conventional therapy for 14 days	Co-enzyme A, vitamin, mecobalamin tablets, Lipo PGE, DXM	PTATC, symptoms
Zhang[56]	ISSHL patients 2005 version	I:38(15–79) C:40(8–60)	86	55.8	Tongqiao Huoxue decoction, 100 mL each time, orally, three times daily plus the same conventional therapy for 12 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, batroxobin, DXM	PTATC

Table 1. continued

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Men (%)	Intervention	Control	Outcomes
Zhang[57]	ISSHL patients Guide version	I:NR C:NR	86	53.5	Longdan Xiegan decoction plus the same conventional therapy for 20 days	ATP, co-enzyme A, vitamin, DXM, HBO	PTATC
Zhang[58]	ISSHL patients Otorhinolaryngology diagnostics	I:NR C:NR	56	39.3	Tongqiao Huoxue decoction, two dose, daily, orally plus the same conventional therapy for 10 days	ATP, co-enzyme A, vitamin, bullomedil hydrochloride, citicoline, DXM	PTATC
Zhang[59]	ISSHL patients 2005 version	I:16–68 C:17–66	60	63.3	Longdan Xiegan decoction, one dose divided into twice daily, orally plus the same conventional therapy for 14 days	Bullomedil hydrochloride	PTATC
Zhou[60]	ISSHL patients 2005 version	I: 48.2 ± 1.9(18–67) C:48.1 ± 2.2(20–71)	80	NR	Practitioner-prescribed herbal formula, one dose divided into twice daily (400 mL), orally plus the same conventional therapy for 10 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, DXM	PTATC
Zhu[61]	ISSHL inpatients and outpatients 1997 version	I: 41.3(24–73) C:42.8(24–72)	70	67.1	Yangxin Zishen decoction plus the same conventional therapy for 14–56 days	Cerebroprotein hydrolysate, flunarizine hydrochloride	PTATC, symptoms
Zhu[62]	ISSHL inpatients 1997 version	I:35.66 ± 13.67 C:38.66 ± 13.74	58	50.0	Mixed Chinese herbs (Tongqiao Huoxue decoction, Tongqiao powder) 100 mL each time, orally, twice daily plus the same conventional therapy for 14 days	Lipo PGE, mecobalamin tablets, nicotinic, acid tablets	PTATC, symptoms, adverse effects
Qiao[63]	ISSHL patients Journal version	I:43.6(21–74) C:41.7(19–68)	97	70.1	Practitioner-prescribed herbal formula, one dose, orally, once daily plus the same conventional therapy for 14 days	Low molecular weight dextran, ATP, co-enzyme A, vitamin, ahylysantinfarctase, DXM, HBO	PTATC
Yan[64]	ISSHL outpatients 1997 version	I:42.6(14–78) C:41(15–77)	115	56.5	Yiqi Conger decoction, 300 mL each time, orally, twice daily plus the same conventional therapy for 14–28 days	Bullomedil hydrochloride	PTATC

Table 1. continued

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Men (%)	Intervention	Control	Outcomes
Wang[62]	ISSHL patients 2005 version	I: 44 ± 17.4(20–65) C: 45 ± 19.6(23–60)	60	51.7	Practitioner-prescribed herbal formula, 300 mL each time, orally, twice daily plus the same conventional therapy for 20 days	ATP, co-enzyme A, nimodipine, HBO	PTATC
Jiang[66]	ISSHL patients 2005 version	I:NR C:NR	94	78.7	I_1: Extract of ginkgo biloba leaf injection, 70 mg each time, once daily plus DXM 10 mg, once daily for 14 days I_2: Extract of ginkgo biloba leaf injection, 70 mg each time, once daily plus Lipo PGE, 10 μg, once daily plus DXM 10 mg, once daily for 14 days	Lipo PGE, DXM	PTATC

I, intervention group; C, control group; NR, not reported, that is, no information in the articles; ISSHL, idiopathic sudden sensorineural hearing loss; PTATC, pure-tone audiometric threshold change; 1997 version, 1997 Chinese Medical Association Otorhinolaryngology criteria; 2005 version, 2005 Chinese Medical Association Otorhinolaryngology criteria; Guide version, Guide of the diagnosis and treatment of ISSHL; Journal version, Chinese Journal of Otorhinolaryngology 1993; 28: 304; ATP, adenosine triphosphatase; DXM, dexamethasone; HBO, hyperbaric oxygen.

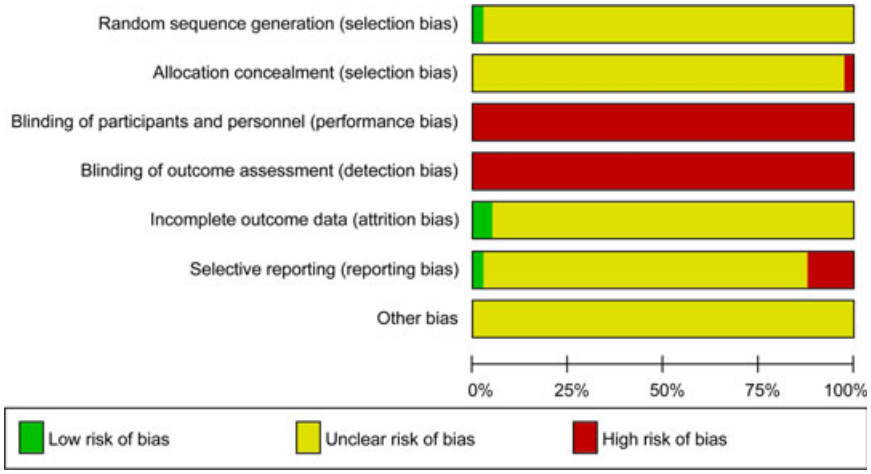


Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

depression (risk ratio −0.56, 95% confidence interval −2.13 to 1.01) after 14-day treatment.[61]

Adverse effects. Adverse effects were reported in only two trials. One stated that none had occurred during treatment session[62] and the other mentioned adverse effects in CHM group, in which two participants suffered more stool and recovered after reducing dosage or drug withdrawal; three participants complained of abdominal distention which disappeared after taking domperidone instead of CHM.[51]

Discussion

Principal findings

Forty-one trials using the planned comparisons were available for evaluation, but meta-analysis was impossible due to the heterogeneity of participants and interventions. Among 41 eligible trials, one trial suggested a greater improvement in pure-tone audiometric threshold favouring CHM. 48.8% (20/41) trials demonstrated a potential positive effect on proportion of participants with improvement in pure-tone audiometric threshold, and 50.0% (6/12) showed CHM seemed to exert a beneficial effect on improvement in tinnitus. At present, these data do not provide conclusive and high-quality evidence to judge the effect and safety of CHM for ISSHL. Given the sources of potential bias, further evidence is required to confirm these trends.

Limitations

There were some limitations in this review. Firstly, all trials were methodologically weak and at high risk of bias. Of 41 trials, only one provided information on the method of randomisation and allocation concealment. No trial conducted blinding and mentioned sample size estimation. Furthermore, there was a considerable clinical heterogeneity in Chinese herbs investigated in the review. A wide range of Chinese herbs were covered, including 29 Chinese herbal formula, seven Chinese herbal powders, five herbal extract injections and three Chinese herbal pills. Thus, it is impossible to synthesise the data into meta-analysis and conduct subgroup analysis to explore the effect of different regimens. In addition, there is inadequate information about a quality standard for the manufacturing of CHM, and therefore, the ingredients and their composition are not standardised. In particular, in view of high rate of spontaneous recovery from ISSHL,[1] there is a likelihood of bias because of the various times that participants were included in these trials. Moreover, there was limited evidence of safety and long-term effect of CHM due to lack of follow-up performance and the inadequate reporting of adverse effects, respectively. Consequently, great caution should be exercised when interpreting the conclusions of this review.

Implications for further research

More rigorous multicentre, larger, adequately powered randomised clinical trials that evaluate CHM for ISSHL are warranted to provide higher-quality evidence. Any future trials would need to state the process of random sequence generation, adequately conceal the allocation of treatment, employ effective and explicit blinding and make a clear description of dropout and withdrawal. Data should be analysed according to intention-to-treat principles. Information about manufacturing method of CHM and their ingredients should be provided sufficiently. Participants should be recruited with clear entry criteria and followed up for long time with clear outcome measures including quality

Table 2. Effect estimates of Chinese herbal medicine for idiopathic sudden sensorineural hearing loss in randomised clinical trials

Outcomes or subgroups	No. of studies	No. of participants	Effect estimate	Study ID
Mean improvement of pure-tone audiometric threshold (MD, 95%CI)				
Chinese herbal medicine plus conventional therapy *versus* the same conventional therapy	3	282		
Xuesaitong injection plus conventional therapy *versus* the same conventional therapy	1	154	−5.00 [−12.23, 2.23]	Pan[37]
Ginkgo-damole injection plus conventional therapy *versus* the same conventional therapy	1	154	−4.00 [−11.70, 3.70]	Pan[37]
Yangxin Zishen decoction plus conventional therapy *versus* the same conventional therapy	1	70	−26.17[−29.15, −23.19]	Zhu[61]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	58	−2.74 [−7.57, 2.09]	Zhu[62]
Proportion of participants with improvement in pure-tone audiometric threshold (RR, 95%CI)				
Chinese herbal medicine *versus* conventional therapy	1	60		
Tongqiao Conger decoction *versus* betahistine mesylate	1	60	1.08 [0.88, 1.32]	Si[40]
Chinese herbal medicine plus conventional therapy *versus* the same conventional therapy	40	3,500		
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	117	1.35 [1.08, 1.67]	Chen[26]
Practitioner-prescribed Zishen Yangxin Huayu decoction plus conventional therapy *versus* the same conventional therapy	1	60	1.60 [1.07, 2.39]	Cui[27]
Erlong 2 Powder plus Lipo PGE plus vitamin *versus* Lipo PGE plus vitamin	1	76	1.31 [1.03, 1.67]	Duan[28]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	226	1.05 [0.90, 1.22]	Guan[29]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	226	0.91 [0.80, 1.04]	Guan[29]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	65	1.16 [0.92, 1.45]	Li[30]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	60	1.64 [1.07, 2.53]	Liang[31]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	100	1.22 [1.01, 1.47]	Liang[32]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	60	1.44 [0.97, 2.12]	Liu[33]
Yishen Zhilong powder plus conventional therapy *versus* the same conventional therapy	1	68	1.38 [0.89, 2.15]	Liu[34]
Longdan Xiegan decoction plus conventional therapy *versus* the same conventional therapy	1	92	1.36 [1.08, 1.72]	Liu[35]

Table 2. continued

Outcomes or subgroups	No. of studies	No. of participants	Effect estimate	Study ID
Practitioner-prescribed herbal formula plus Lipo PGE *versus* Lipo PGE	1	188	1.08 [0.95, 1.22]	Luo[36]
Xuesaitong injection plus conventional therapy *versus* the same conventional therapy	1	154	1.34 [0.98, 1.84]	Pan[37]
Ginkgo-damole injection plus conventional therapy *versus* the same conventional therapy	1	154	1.31 [0.96, 1.80]	Pan[37]
Tongqiao Huoxue powder plus Lipo PGE plus vitamin *versus* Lipo PGE plus vitamin	1	80	1.26 [0.98, 1.62]	Shao[38]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	80	1.26 [0.98, 1.62]	Shi[39]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	106	1.20 [1.02, 1.42]	Sun[41]
Mixed Chinese herbs plus corticosteroid *versus* corticosteroid	1	66	1.23 [0.98, 1.55]	Sun[42]
Xingqi Huoxue Tongqiao decoction plus conventional therapy *versus* the same conventional therapy	1	50	1.58 [1.03, 2.40]	Wang[43]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	50	1.36 [0.90, 2.05]	Wang[44]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	72	1.18 [0.95, 1.47]	Wei[45]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	60	1.38 [1.01, 1.90]	Wu[46]
Shugan Tongqiao decoction plus fluorine gonadorelin plus duxil *versus* fluorine gonadorelin plus duxil	1	60	1.41 [0.98, 2.02]	Yang[47]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	120	1.29 [1.03, 1.62]	Yang[48]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	145	1.32 [1.11, 1.57]	Yin[49]
Practitioner-prescribed Conger decoction plus conventional therapy *versus* the same conventional therapy	1	72	1.24 [1.01, 1.51]	Yu[50]
Tuqiao Tonglong decoction plus conventional therapy *versus* the same conventional therapy	1	65	1.49 [1.12, 1.98]	Yu[51]
Kangnaoshuai capsule plus conventional therapy *versus* the same conventional therapy	1	100	1.50 [1.21, 1.86]	Yuan[52]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	78	1.51 [1.13, 2.03]	Zhang[53]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	120	1.19 [0.98, 1.44]	Zhang[58]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	48	1.42 [0.96, 2.10]	Zhang[55]
Tongqiao Huoxue decoction plus conventional therapy *versus* the same conventional therapy	1	86	1.09 [0.97, 1.23]	Zhang[56]

Table 2. continued

Outcomes or subgroups	No. of studies	No. of participants	Effect estimate	Study ID
Longdan Xiegan decoction plus conventional therapy *versus* the same conventional therapy	1	86	1.12 [0.91, 1.37]	Zhang[57]
Huoxue Tongqiao decoction plus conventional therapy *versus* the same conventional therapy	1	56	1.20 [0.91, 1.59]	Zhang[58]
Longdan Xiegan decoction plus bullomedil hydrochloride *versus* bullomedil hydrochloride	1	60	0.99 [0.71, 1.38]	Zhang[59]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	80	1.38 [1.09, 1.74]	Zhou[60]
Yangxin Zishen decoction plus conventional therapy *versus* the same conventional therapy	1	70	1.60 [0.98, 2.59]	Zhu[61]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	58	1.26 [1.02, 1.55]	Zhu[62]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	97	1.39 [1.08, 1.79]	Qiao[63]
Yiqi Conger decoction plus bullomedil hydrochloride *versus* bullomedil hydrochloride	1	115	1.23 [1.00, 1.52]	Yan[64]
Practitioner-prescribed herbal formula plus conventional therapy *versus* conventional therapy	1	60	1.37 [1.01, 1.86]	Wang[65]
Extract of ginkgo biloba leaves injection plus dexamethasone *versus* dexamethasone plus Lipo PGE	1	94	1.45 [1.05, 2.00]	Jiang[66]
Extract of ginkgo biloba leaves injection plus Lipo PGE plus dexamethasone *versus* Lipo PGE plus dexamethasone	1	94	1.01 [0.68, 1.51]	Jiang[66]
Proportion of participants with improvement of tinnitus (RR, 95%CI)				
Chinese herbal medicine plus conventional therapy *versus* the same conventional therapy	12	929		
Practitioner-prescribed Zishen Yangxin Huayu Decoction plus conventional therapy *versus* the same conventional therapy	1	60	1.64 [1.14, 2.37]	Cui[27]
Erlong 2 Powder plus Lipo PGE plus vitamin *versus* Lipo PGE plus vitamin	1	76	2.00 [1.22, 3.27]	Duan[28]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	60	1.54 [1.01, 2.34]	Liang[31]
Practitioner-prescribed herbal formula plus conventional therapy *versus* the same conventional therapy	1	60	1.54 [1.01, 2.34]	Liu[33]
Longdan Xiegan decoction plus conventional therapy *versus* the same conventional therapy	1	92	1.25 [1.04, 1.50]	Liu[35]
Practitioner-prescribed herbal formula plus Lipo PGE *versus* Lipo PGE	1	188	1.58 [1.19, 2.09]	Luo[36]
Tongqiao Huoxue powder plus Lipo PGE plus vitamin *versus* Lipo PGE plus vitamin	1	80	1.25 [0.92, 1.69]	Shao[38]

Table 2. continued

Outcomes or subgroups	No. of studies	No. of participants	Effect estimate	Study ID
Practitioner-prescribed Conger decoction plus conventional therapy *versus* the same conventional therapy	1	72	1.40 [1.00, 1.96]	Yu[50]
Tuqiao Tonglong decoction plus conventional therapy *versus* the same conventional therapy	1	65	1.40 [1.00, 1.96]	Yu[51]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	48	1.37 [0.91, 2.06]	Zhang[55]
Yangxin Zishen decoction plus conventional therapy *versus* the same conventional therapy	1	70	1.64 [0.87, 3.08]	Zhu[61]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	58	0.95 [0.70, 1.29]	Zhu[62]
Proportion of participants with improvement of dizziness (RR, 95%CI)				
Chinese herbal medicine plus conventional therapy *versus* the same conventional therapy	6	559		
Erlong 2 powder plus Lipo PGE plus vitamin *versus* Lipo PGE plus vitamin	1	76	8.07 [1.21, 53.58]	Duan[28]
Longdan Xiegan decoction plus conventional therapy *versus* the same conventional therapy	1	92	1.06 [0.93, 1.20]	Liu[35]
Practitioner-prescribed herbal formula plus Lipo PGE *versus* Lipo PGE	1	188	1.03 [0.89, 1.19]	Luo[36]
Tongqiao Huoxue powder plus Lipo PGE plus vitamin *versus* Lipo PGE plus vitamin	1	80	1.30 [0.96, 1.78]	Shao[38]
Tuqiao Tonglong decoction plus conventional therapy *versus* the same conventional therapy	1	65	1.00 [0.89, 1.12]	Yu[51]
Mixed Chinese herbs plus conventional therapy *versus* the same conventional therapy	1	58	0.33 [0.13, 0.81]	Zhu[62]
Scores of depression and anxiety (MD, 95%CI)				
Chinese herbal medicine plus conventional therapy *versus* the same conventional therapy	1	70		
Yangxin Zishen decoction plus conventional therapy *versus* the same conventional therapy	1	70	Depression: −0.56 [−2.13,1.01] Anxiety: −2.80 [−4.80, −0.80]	Zhu[61]

of life. Adverse effects and the cost-benefit of CHM should be reported. Studies should be run and managed in accordance with Consolidated Standards of Reporting Trials statement so as to promote the internal and external validity.[69]

Conclusion

Currently, there appears a limited role for CHM to significantly contribute to improving hearing in people with ISSHL. The current evidence from the poor methodological quality of trials is insufficiently robust to support the clinical use of CHM for ISSHL. Therefore, further rigorous trials with high quality are needed to increase the strength of evidence.

Keypoints

- At present, there is insufficient evidence to judge the effect and safety of Chinese herbal medicine for idiopathic sudden sensorineural hearing loss.
- More rigorous multicenter, larger, adequately powered randomised clinical trials that evaluate Chinese herbal medicine for idiopathic sudden sensorineural hearing loss are warranted.

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Conflict of interests

All authors declare that there is no conflict of interests.

Contributions

Su CX conceived and designed the review, searched and selected studies, extracted data and analysed data, assessed the methodological quality and drafted the manuscript. Yan LJ searched and selected studies, extracted data and assessed the methodological quality. Lewith G made substantial revisions to the article. Liu JP conceived and designed the review and made substantial revisions to the article. All authors have approved the final submitted version.

References

1 Stachler R.J., Chandrasekhar S.S., Archer S.M. *et al.* (2012) Clinical practice guideline: sudden hearing loss. *Otolaryngol. Head Neck Surg.* **146**(Suppl. 3), S1–S35

2 Hughes G.B., Freedman M.A., Haberkamp T.J. *et al.* (1996) Sudden sensorineural hearing loss. *Otolaryngol. Clin. North Am.* **29**, 393–405

3 Stokroos R.J., Albers F.W. & Van Cauwenberge P. (1996) Diagnosis and treatment of idiopathic sudden sensorineural hearing loss (ISSHL): a survey in the Netherlands and Flanders. *Acta Otorhinolaryng. Belg.* **50**, 237–245

4 Klemm E., Deutscher A. & Mösges R. (2009) A present investigation of the epidemiology in idiopathic sudden sensorineural hearing loss. *Laryngorhinootologie* **88**, 524–527

5 Thurmond M. & Amedee R.G. (1998) Sudden sensorineural hearing loss: etiologies and treatments. *J. La State Med. Soc.* **150**, 200–203

6 Yoon T.H., Paparella M.M., Schachern P.A. *et al.* (1990) Histopathology of sudden hearing loss. *Laryngoscope* **100**, 707–715

7 Mösges R., Köberlein J., Erdtracht B. *et al.* (2008) Quality of life in patients with idiopathic sudden hearing loss: comparison of different therapies using the Medical Outcome Short Form (36) Health Survey questionnaire. *Otol. Neurotol.* **29**, 769–775

8 Sano H., Okamoto M., Ohhashi K. *et al.* (2013) Quality of life reported by patients with idiopathic sudden sensorineural hearing loss. *Otol. Neurotol.* **34**, 36–40

9 Carlsson P.I., Hall M., Lind K.J. *et al.* (2011) Quality of life, psychosocial consequences, and audiological rehabilitation after sudden sensorineural hearing loss. *Int. J. Audiol.* **50**, 139–144

10 Rauch S.D. (2008) Idiopathic sudden sensorineural hearing loss. *N. Engl. J. Med.* **359**, 833–840

11 Bennett M.H., Kertesz T., Perleth M. *et al.* (2012) Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus. *Cochrane Database Syst. Rev.* **10**, CD004739

12 Agarwal L. & Pothier D.D. (2009) Vasodilators and vasoactive substances for idiopathic sudden sensorineural hearing loss. *Cochrane Database Syst. Rev.* **4**, CD003422

13 Nosrati-Zarenoe R. & Hultcrantz E. (2012) Corticosteroid treatment of idiopathic sudden sensorineural hearing loss: randomized triple-blind placebo-controlled trial. *Otol. Neurotol.* **33**, 523–531

14 Awad Z., Huins C. & Pothier D.D. (2012) Antivirals for idiopathic sudden sensorineural hearing loss. *Cochrane Database Syst. Rev.* **8**, CD006987

15 Spear S.A. & Schwartz S.R. (2011) Intratympanic steroids for sudden sensorineural hearing loss: a systematic review. *Otolaryngol. Head Neck Surg.* **145**, 534–543

16 Yao C.P. (2010) *Yellow Emperor's Inner Canon of Medicine*. Zhonghua Book Company, Shanghai

17 Hu L.S. & Li F.C. (2004) *Otolaryngology of traditional Chinese medicine*. China Press of Traditional Chinese Medicine, Beijing

18 Wang D. & Li S.J. (2008) The effect of ligustrazine on treatment of sudden hearing loss. *Chin. Otorhinolaryng. J. Integr. Med.* **16**, 216–217

19 Li W.H. & Yao W.H. (2000) The effect of high doses of ligustrazine on treatment of sudden hearing loss. *Chin. J. Mod. Med.* **10**, 92

20 Wang Q. (2009) The effect of Ginkgodipyidamolum on treatment of 32 cases with sudden hearing loss. *Mod. J. Integr. Tradit. Chin. West. Med.* **18**, 1029

21 Shi H.X. & Hai Y. (2005) The effect of Ginkgodipyidamolum on treatment of sudden hearing loss. *J. Chin. Otolaryngol.* **2**, 174–175

22 Zhu J.G. (2008) Ginkgodipyidamolum on treatment of sudden hearing loss. *Mod. J. Integr. Tradit. Chin. West. Med.* **17**, 5593–5594

23 Wang H.K., Tian W.Q., Li Q.W. *et al.* (2009) Ginkgodipyidamolum on treatment of sudden hearing loss. *Chin. Pr. Med.* **4**, 132–133

24 Li M.L. & Lai Y.S. (2009) Ginkgodipyidamolum on treatment of 48 cases with sudden hearing loss. *J. Strait Pharm.* **21**, 142–143

25 Higgins J.P.T. & Green S. (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0 the cochrane collaboration. URL http://www.cochrane-handbook.org [accessed on March 2011]

26 Chen P. (2009) Effect of integrated traditional Chinese and western medicine based on syndrome differentiation on the treatment of sudden hearing loss. *Mod. J. Integr. Tradit. Chin. West. Med.* **18**, 3325–3326

27 Cui Q.X. (2010) Effect of integrated traditional Chinese and western medicine on the treatment of 30 cases with sudden hearing loss. *Guide Chin. Med.* **8**, 82–83

28 Duan X.H. (2008) *Effect of Erlong 2 powder on treatment of sudden hearing loss*. Postgraduate Thesis, Heilongjiang Univ Chin Med, Haerbin

29 Guan S.Y., Li W.H., Luo T.F. *et al.* (2009) Clinical effect analysis of integrated traditional Chinese and western medicine on the treatment of sudden hearing loss. *Chin. J. Mod. Drug Appl.* **3**, 151–152

30 Li Y.X., Han L.H., Wu H. *et al.* (2008) Effect of integrated traditional Chinese and western medicine on the treatment of sudden hearing loss. *Med. Innovat. Res.* **5**, 8–10

31 Liang Q.J. & Lu J.G. (2003) Effect of integrated traditional Chinese and western medicine on the treatment of 30 cases with sudden hearing loss. *J. New Chin. Med.* **38**, 48–49

32 Liang S.Q. (2011) Effect of integrated traditional Chinese and western medicine on the treatment of sudden hearing loss. *Chin. Foreign Med. Res.* **9**, 54–55

33 Liu Q., Liu M. & Du F.L. (2001) Effect of integrated traditional Chinese and western medicine on the treatment of 30 cases with sudden hearing loss. *Chin. J. Integr. Tradit. West. Med.* **21**, 869–871

34 Liu S. (2005) *Effect of treatment based on differentiation diagnosis on sudden hearing loss with kidney essence deficiency*. Postgraduate Thesis, Liaoning Univ Tradit Chin Med, Shenyang

35 Liu Y., Jiang Y.S. & Yao W. (2011) Clinical research on integrated traditional Chinese and western medicine for treatment of 48 cases with sudden hearing loss. *Jiangsu J. Tradit. Chin. Med.* **43**, 34–35

36 Luo K.Q., Hu K., Zhang H. *et al.* (2004) Clinical observation on the therapeutic effects of an integrative medicine therapy on the accompanied tinnitus and vertigo with sudden deafness. *Chin. J. Otolaryngol. Integr. Tradit. West. Med.* **12**, 66–68

37 Pan L.M., Hu W.M., Su L.Z. *et al.* (2008) Effect of vasodilator substance of Traditional Chinese medicine for the treatment of sudden hearing loss. *Chin. Otorhinolarngol. J. Integr. Med.* **16**, 281–284

38 Shao J.N. (2012) *Clinical study of Tongqiao Huoxue Granule in the treatment of sudden deafness*. Postgraduate Thesis, Heilongjiang Univ Chin Med, Haerbin

39 Shi W.D. (2006) Effect of integrated traditional Chinese and western medicine on the treatment of 40 cases with sudden hearing loss. *Zhejiang J. Integr. Tradit. Chin. West. Med.* **16**, 642–643

40 Si X.W. & Li Y.C. (2012) Clinical research on treating sudden sensorineural hearing loss with the Conger Tongqiao decoction. *Clin. J. Chin. Med.* **4**, 23–25

41 Sun M.Q. & Zhang H.W. (2005) Effect of integrated traditional Chinese and western medicine on the treatment of 54 cases with sudden hearing loss. *Chin. Naturopathy* **13**, 13–15

42 Sun Y.F., Li S.H. & Zhou X.J. (2010) Research on 68 Cases of Sudden Deafness Treated with Integrated Traditional Chinese and Western Medicine. *Clin. Med. Eng.* **17**, 78–79

43 Wang R.X. (2002) *Clinical research on integrated traditional Chinese and western medicine for the treatment of 30 cases with sudden hearing loss*. Postgraduate Thesis, Shandong Univ Chin Med, Jinan

44 Wang X.H. (2011) Clinical observation of integrated traditional Chinese and western medicine for the treatment of 25 cases with sudden hearing loss. *J. Pr. Tradit. Chin. Med.* **27**, 312–313

45 Wei J.Z. & Cong P. (2002) Effect of Huoxue Huayu on the treatment of 72 cases with sudden hearing loss. *J. Zhejiang Chin. Med. Univ.* **26**, 26

46 Wu H.L. (2012) Clinical observation of integrated traditional Chinese and western medicine on the treatment of 35 cases with sudden hearing loss. *J. New Chin. Med.* **44**, 61–62

47 Yang D., Li X. & Liu H.X. (2006) Analysis of the sudden hearing loss in 60 patients. *J. Tianjin Univ. Tradit. Chin. Med.* **25**, 22–24

48 Yang L. (2011) Observation on the treatment of sudden deafness in the integrative medicine. *Clin. J. Chin. Med.* **3**, 19–20

49 Yin Y.X., Bao J.C. & Yang Z.Y. (2012) Clinical effect analysis of integrated traditional Chinese and western medicine on the treatment of sudden hearing loss. *Chin. J. Ethnomed. Ethnopharm.* **21**, 122–123

50 Yu S.J. (2006) Effect of integrated traditional Chinese and western medicine on the treatment of sudden hearing loss. *Med. Inform.* **19**, 1456–1457

51 Yu Y.M. & Pei H.B. (2006) 35 cases of sudden deafness with combined treatment of traditional chinese medicine and western medicine. *J. Henan Univ. Chin. Med.* **5**, 41–42

52 Yuan K. & Liu B. (2000) Kangnaoshuai capsule for the treatment of 50 cases with sudden hearing loss. *Her Med.* **19**, 461–462

53 Zhang D.W. (1994) Effect of integrated traditional Chinese and western medicine on the treatment of 40 cases with sudden hearing loss. *Huanghe Med.* **3**, 12

54 Zhang D.K., Li Z.X., Jiang W. *et al.* (2011) Clinic effect observation of traditional Chinese medicine and western medicine combined hyperbaric oxygen in treatment of sudden hearing loss. *Clin. J. Med. Off.* **36**, 544–546

55 Zhang M.R. (2012) Clinical effect observation of integrated traditional Chinese and western medicine for the treatment of sudden hearing loss. *J. Sichuan Tradit. Chin. Med.* **30**, 119–120

56 Zhang S.L. (2010) Clinical analysis of Huoxue Tongqiao decoction for the treatment of 86 cases with sudden hearing loss. *Inner Mongolia J. Tradit. Chin. Med.* **29**, 37–38

57 Zhang S.L. (2012) Clinical effect analysis of integrated traditional Chinese and western medicine for the treatment of sudden hearing loss. *Chin. Foreign Med. Treat.* **31**, 81

58 Zhang X.L. & Zhang Z.Z. (2011) Observation of integrated traditional Chinese and western medicine for the treatment of 56 cases with sudden hearing loss. *Chin. Commun. Doct.* **13**, 192

59 Zhang Z.H., Li S.Q., Shi X.P. *et al.* (2009) Clinical observation of integrated traditional Chinese and western medicine on the treatment of sudden hearing loss accompanied with dizziness. *J. Otolaryng. Tradit. Chin. Med. Res.* **8**, 18–19

60 Zhou R.J. (2012) Clinical effect analysis of integrated traditional Chinese and western medicine for the treatment of 38 cases with sudden hearing loss. *World Health Digest. Med. Period.* **9**, 411

61 Zhu M., Liu L.X., Huang X.B. *et al.* (2007) Effect of integrated traditional Chinese and western medicine on the treatment of 55 cases with sudden hearing loss. *J. Fujian Coll. Tradit. Chin. Med.* **17**, 3–5

62 Zhu X.J. (2011) *Effect observation on Tongqiao Huoxue decoction in combination with Tongqi powder for sudden hearing loss of qi stagnation and blood stasis*. Postgraduate Thesis, Fujian Univ Chin Med, Fuzhou

63 Qiao Z.Q., Wang R.T. & Wang X.H. (1999) Effect of integrated traditional Chinese and western medicine on the treatment of 52 cases with sudden hearing loss. *Chin. J. Integr. Tradit. West. Med.* **19**, 119–120

64 Yan X.L. (2011) Clinical effect observation of integrated traditional Chinese and western medicine on the treatment of 58 cases with sudden hearing loss. *J. Sichuan Tradit. Chin. Med.* **29**, 115
65 Wang W.G., Pu W., Bian X. *et al.* (2008) Investigation on the effect of Qi-boosting blood-quickening method on free radicals and its mechanism underlying the therapeutic effect on sudden hearing loss. *Chin. Otorhinolaryng. J. Integ. Med.* **16**, 4–7
66 Jiang J.P., Wang S.Y. & Tong K. (2011) Synergic effect of Alprostadil injection and ginaton in treating sudden deafness. *J. Clin. Otorhinolaryng. Head. Neck.* **23**, 597–599
67 Otorhinolaryngology of Chinese Medical Association. & editorial board of Chinese Journal of Otolaryngology. (1997) PLEASE suggest whether the phrase criteria of effectiveness of sudden hearing loss. *Chin. J. Otorhinolaryng.* **32**, 72
68 Editorial board of Chinese Journal of Otolaryngology. & Otorhinolaryngology Head and Neck Surgery of Chinese Medical Association. (2006) Guideline of diagnosis and treatment of sudden hearing loss (2005, Jinan). *Chin. J. Otorhinolaryng. Head Neck* **41**, 325
69 Schulz K.F., Altman D.G., Moher D. *et al.* (2011) CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Int. J. Surg.* **9**, 672–677

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Search strategy.