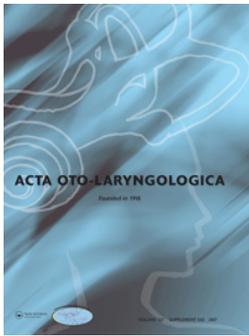


The effect of initial treatment on hearing prognosis in idiopathic sudden sensorineural hearing loss : a nationwide survey in Japan

著者別名	原 晃
journal or publication title	Acta oto-laryngologica
volume	137
number	sup565
page range	S30-S33
year	2017
権利	(C) 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.
URL	http://hdl.handle.net/2241/00146719

doi: 10.1080/00016489.2017.1296970



The effect of initial treatment on hearing prognosis in idiopathic sudden sensorineural hearing loss: a nationwide survey in Japan

Masahiro Okada, Naohito Hato, Shin-ya Nishio, Ryosuke Kitoh, Kaoru Ogawa, Sho Kanzaki, Michihiko Sone, Satoshi Fukuda, Akira Hara, Tetsuo Ikezono, Kotaro Ishikawa, Satoshi Iwasaki, Kimitaka Kaga, Seiji Kakehata, Atsushi Matsubara, Tatsuo Matsunaga, Takaaki Murata, Yasushi Naito, Takashi Nakagawa, Kazunori Nishizaki, Yoshihiro Noguchi, Hajime Sano, Hiroaki Sato, Mikio Suzuki, Hideo Shojaku, Haruo Takahashi, Hidehiko Takeda, Tetsuya Tono, Hiroshi Yamashita, Tatsuya Yamasoba & Shin-ichi Usami

To cite this article: Masahiro Okada, Naohito Hato, Shin-ya Nishio, Ryosuke Kitoh, Kaoru Ogawa, Sho Kanzaki, Michihiko Sone, Satoshi Fukuda, Akira Hara, Tetsuo Ikezono, Kotaro Ishikawa, Satoshi Iwasaki, Kimitaka Kaga, Seiji Kakehata, Atsushi Matsubara, Tatsuo Matsunaga, Takaaki Murata, Yasushi Naito, Takashi Nakagawa, Kazunori Nishizaki, Yoshihiro Noguchi, Hajime Sano, Hiroaki Sato, Mikio Suzuki, Hideo Shojaku, Haruo Takahashi, Hidehiko Takeda, Tetsuya Tono, Hiroshi Yamashita, Tatsuya Yamasoba & Shin-ichi Usami (2017) The effect of initial treatment on hearing prognosis in idiopathic sudden sensorineural hearing loss: a nationwide survey in Japan, *Acta Oto-Laryngologica*, 137:sup565, S30-S33, DOI: [10.1080/00016489.2017.1296970](https://doi.org/10.1080/00016489.2017.1296970)

To link to this article: <http://dx.doi.org/10.1080/00016489.2017.1296970>



© 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



[View supplementary material](#)



Published online: 31 Mar 2017.



[Submit your article to this journal](#)



Article views: 311



[View related articles](#)



View Crossmark data [↗](#)



Citing articles: 1 View citing articles [↗](#)

Full Terms & Conditions of access and use can be found at
<http://www.tandfonline.com/action/journalInformation?journalCode=ioto20>

RESEARCH ARTICLE



The effect of initial treatment on hearing prognosis in idiopathic sudden sensorineural hearing loss: a nationwide survey in Japan

Masahiro Okada^a, Naohito Hato^a, Shin-ya Nishio^b, Ryosuke Kitoh^b, Kaoru Ogawa^c, Sho Kanzaki^c, Michihiko Sone^d, Satoshi Fukuda^e, Akira Hara^f, Tetsuo Ikezono^g, Kotaro Ishikawa^h, Satoshi Iwasakiⁱ, Kimitaka Kaga^j, Seiji Kakehata^k, Atsushi Matsubara^l, Tatsuo Matsunaga^j, Takaaki Murata^m, Yasushi Naitoⁿ, Takashi Nakagawa^o, Kazunori Nishizaki^p, Yoshihiro Noguchi^b, Hajime Sano^q, Hiroaki Sato^r, Mikio Suzuki^s, Hideo Shojaku^t, Haruo Takahashi^u, Hidehiko Takeda^v, Tetsuya Tono^w, Hiroshi Yamashita^x, Tatsuya Yamasoba^y and Shin-ichi Usami^b

^aDepartment of Otolaryngology, Ehime University School of Medicine, Toon, Japan; ^bDepartment of Otorhinolaryngology, Shinshu University School of Medicine, Matsumoto, Japan; ^cDepartment of Otorhinolaryngology Head and Neck Surgery, Keio University School of Medicine, Tokyo, Japan; ^dDepartment of Otorhinolaryngology, Nagoya University, Graduate School of Medicine, Nagoya, Japan; ^eDepartment of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan; ^fDepartment of Otolaryngology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; ^gDepartment of Otorhinolaryngology, Saitama School of Medicine, Moroyama, Japan; ^hDepartment of Otolaryngology, Hospital, National Rehabilitation Center for Persons with Disabilities, Tokorozawa, Japan; ⁱDepartment of Otolaryngology, International University of Health and Welfare, Mita Hospital, Tokyo, Japan; ^jDivision of Hearing and Balance Research, National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, Tokyo, Japan; ^kDepartment of Otorhinolaryngology, Yamagata University School of Medicine, Yamagata, Japan; ^lDepartment of Otorhinolaryngology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan; ^mDepartment of Otolaryngology, Gunma University Graduate School of Medicine, Maebashi, Japan; ⁿDepartment of Otolaryngology, Kobe City Medical Center General Hospital, Kobe, Japan; ^oDepartment of Otorhinolaryngology, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan; ^pDepartment of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmacy, Okayama, Japan; ^qDepartment of Otolaryngology, Kitasato University School of Medicine, Sagami, Japan; ^rDepartment of Otorhinolaryngology, Iwate Medical University, Morioka, Japan; ^sDepartment of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Medicine, University of the Ryukyus, Nishihara, Japan; ^tDepartment of Otorhinolaryngology, Head and Neck Surgery, University of Toyama, Toyama, Japan; ^uDepartment of Otolaryngology, Nagasaki University Faculty of Medicine, Nagasaki, Japan; ^vDepartment of Otolaryngology, Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan; ^wDepartment of Otolaryngology, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan; ^xDepartment of Otolaryngology, Yamaguchi University Graduate School of Medicine, Ube, Japan; ^yDepartment of Otolaryngology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

ABSTRACT

Objective: To investigate the hearing prognosis of idiopathic sudden sensorineural hearing loss (SSNHL) treated with different initial therapies.

Methods: Subjects consisted of patients diagnosed with idiopathic SSNHL within 7 days from onset and showing severe hearing loss (≥ 60 dB), who were registered in a Japanese multicenter database between April 2014 and March 2016. Subjects were divided into four groups according to initial therapy: (1) steroids, (2) steroids + Prostaglandins (PGs), (3) intratympanic steroids (ITS), and (4) no steroids. Hearing outcomes were compared among the groups.

Results: In total, 1305 patients were enrolled. The final hearing level and hearing gain of patients treated with steroids + PGs were significantly higher than those of patients treated with steroids alone or no steroids. The ratio of good prognosis (complete recovery or marked improvement) in patients treated with steroids + PGs was higher than that in patients treated with steroids alone or no steroids. There was no difference in the prognosis of patients treated with steroids alone or no steroids.

Conclusion: A large number of patients with idiopathic SSNHL were registered in a multicenter database. PG use in combination with steroid administration was associated with a good hearing prognosis in patients with severe hearing loss.

ARTICLE HISTORY

Received 3 January 2017
Revised 13 February 2017
Accepted 15 February 2017

KEYWORDS

Idiopathic sudden sensorineural hearing; steroid; prostaglandin; intratympanic steroid injection

Introduction

Idiopathic sudden sensorineural hearing loss (SSNHL) is a sensorineural hearing dysfunction of unknown etiology

characterized by the sudden onset and mostly unilateral hearing loss. The latest epidemiological survey of hospitals and clinics in Japan revealed that the incidence of idiopathic

CONTACT Masahiro Okada  okadama@e.hime-u.ac.jp  Department of Otolaryngology, Head and Neck Surgery, Ehime University School of Medicine, 791-0295, Shitsukawa, Toon city, Ehime, Japan; Shin-ichi Usami  usami@shinshu-u.ac.jp  Department of Otorhinolaryngology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan

 Supplemental data for this article can be accessed [here](#).

© 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

SSNHL was 60.9 per 100,000 population [1]. Little is known about the pathogenesis of idiopathic SSNHL, but several treatments have been proposed that cover the possible underlying mechanisms of disease, such as viral infection, intracochlear membrane rupture, and vascular compromise [2,3]. As corticosteroids are known to be efficacious with regard to the inner ear in cases with hearing loss of viral, vascular, autoimmune, endolymphatic hydrops, and other etiologies [4,5], systemic and/or intratympanic corticosteroids have been widely used for the treatment of idiopathic SSNHL. However, the value of corticosteroid treatment for idiopathic SSNHL remains unclear due to related studies being of low methodological quality or based on small study populations [6–8]. Prostaglandins (PGs) are vasoactive agents that have also been used in SSNHL to enhance cochlear blood flow [9–11]. Although PGs have shown benefits as vasodilators and inhibitors of platelet aggregation, the value of PG treatment for idiopathic SSNHL is also unclear because of the high risk of bias and small sample sizes [12].

Five single-year nationwide surveys of idiopathic SSNHL have been conducted by the Research Committees of Ministry of Health and Welfare in Japan. As part of these surveys, a multicenter database was constructed, and large numbers of patients with idiopathic SSNHL ($N = 3419$) have been registered. In this study, we investigated the effects of initial therapy on hearing prognosis in idiopathic SSNHL based on an analysis of this survey data.

Material and methods

The subjects for this analysis were patients registered in the multicenter database (involving 30 university hospitals and medical centers) between April 2014 and March 2016. Information regarding the patients' sex, age, date of birth, days from onset to visit, the incidence of vertigo/dizziness, the incidence of diabetes mellitus, the use of systemic steroids, PGs, and intratympanic steroid (ITS) injections, and initial and final audiograms were obtained. Idiopathic SSNHL was defined according to the criteria established by the Sudden Deafness Research Committee of the Ministry of Health and Welfare, Japan (Table 1). From the audiogram data, the grade of the initial audiogram (Table 2) and the recovery rate (Table 3), as defined by the Ministry of Health and Welfare in Japan, were obtained.

Table 1. Criteria for the diagnosis of idiopathic SSNHL.

Main symptoms	
Sudden onset	
Sensorineural hearing loss, usually severe	
Unknown etiology	
For reference	
Hearing loss (hearing loss of 30 dB or more over three consecutive frequencies)	
Sudden onset of hearing loss, but may progressively deteriorate over 72 h	
No history of recurrent episodes	
Unilateral hearing loss, but may be bilateral at onset	
May be accompanied by tinnitus	
May be accompanied by vertigo, nausea, and/or vomiting, without recurrent episodes	
No cranial nerve symptoms other than from the cranial nerve VIII	
Definite diagnosis; all of the above main symptoms are present	

To compare the prognosis for hearing outcome according to initial treatment, we divided the patients into four groups: (1) patients who were administered systemic corticosteroids as initial therapy (steroids group), (2) patients who were administered systemic corticosteroids and PGs as initial therapy (steroids + PGs group), (3) patients who were administered ITS as initial therapy without systemic corticosteroid administration (ITS group), and (4) patients who were not administered corticosteroids, ITS, or PGs (no steroids group). Inclusion criteria consisted of a diagnosis of idiopathic SSNHL within 7 days from onset and severe hearing loss (Grade 3 or Grade 4). We excluded patients who received ITS therapy as salvage therapy, so that 89 patients from the steroids group and 73 patients from the steroids + PGs group were excluded from this study. We also excluded patients whose data were incomplete.

The study protocol was approved by the ethics review committees of Ehime University and other participating institutional ethical committees.

Pearson's chi-squared test was used to analyze the prognosis for hearing. Other analyses were performed using the *t*-test. All analyses were performed using JMP version 12.0.1 (SAS Institute Inc., Cary, NC).

Results

A total of 1305 patients were enrolled in this study. The steroids group included 795 patients, the steroids + PGs group included 375 patients, the ITS group included 70 patients, and the no steroids group included 65 patients. The clinical characteristics of the four groups are summarized in Table 4. There were no significant differences in gender, affected side, incidence of vertigo/dizziness, days from onset to visit, or initial hearing level among the groups. The steroids + PGs group was younger than the other groups ($p < .05$ vs. steroids group, $p < .01$ vs. ITS and no steroids groups), and the steroids group was younger than the ITS and no steroids groups ($p < .05$). The incidences of diabetes mellitus in the ITS and no steroids groups were higher than those in the other groups ($p < .01$).

Table 2. Criteria for the grading of hearing loss in idiopathic SSNHL.

Grade	Criteria
1	PTA <40 dB
2	40 dB \leq PTA <60 dB
3	60 dB \leq PTA <90 dB
4	90 dB \leq PTA

PTA: arithmetic mean of five frequencies (250, 500, 1000, 2000, and 4000 Hz).

Table 3. Hearing improvement criteria for idiopathic SSNHL as defined by the Ministry of Health and Welfare in Japan.

Hearing improvement status	Criteria
Complete recovery	All five frequencies of the final audiogram are 20 dB or less, or improvement to the same degree of hearing in the unaffected side
Marked improvement	PTA improvement \geq 30 dB
Slight improvement	10 dB \leq PTA improvement <30 dB
No change	PTA improvement <10 dB

PTA: arithmetic mean of five frequencies (250, 500, 1000, 2000, and 4000 Hz).

Table 4. The clinical characteristics of patients.

	Steroids group	Steroids + PGs group	ITS group	No steroids group
No. of patients	795	375	70	65
Gender (male/female)	435/360	183/192	42/28	31/34
Affected side (right/left)	388/407	175/200	40/30	30/35
Age (years)				
Mean \pm SEM	55.4 \pm 17.7 ^a	53.3 \pm 17.0 ^a	59.9 \pm 14.5	63.0 \pm 15.9
Incidence of vertigo/dizziness	38.6%	37.1%	27.9%	39.4%
Incidence of diabetes	17.5%	18.8%	54.4% ^b	43.8% ^b
Days from onset to visit	2.8 \pm 1.9	2.6 \pm 1.8	3.1 \pm 2.0	2.7 \pm 2.0
Initial hearing level				
Mean \pm SEM (dB)	85.6 \pm 15.7	84.8 \pm 15.3	84.4 \pm 15.1	84.8 \pm 17.6
(Grade 3/Grade 4)	488/307	241/134	47/23	38/27

^a $p < .05$ vs. ITS group and $p < .01$ vs. no steroids group.

^b $p < .01$ vs. steroids group and steroids + PGs group.

Table 5. Hearing outcome of patients.

	Steroids group	Steroids + PGs group	ITS group	No steroids group
Final hearing level				
Mean \pm SEM (dB)	52.7 \pm 29.1	47.0 \pm 27.7 ^a	48.7 \pm 25.9	57.2 \pm 29.5
Hearing gain				
Mean \pm SEM (dB)	33.0 \pm 23.4	37.8 \pm 23.0 ^a	35.7 \pm 20.2 ^b	27.7 \pm 20.4
Ratio of good prognosis (Complete recovery + marked improvement)	479 (60.3%)	263 (70.1%) ^c	44 (62.8%)	35 (53.8%)

^a $p < .01$ vs. steroids group and no steroids group.

^b $p < .05$ vs. no steroids group.

^c $p < .01$ vs. steroids group and no steroids group.

The hearing prognoses for the four groups are shown in Table 5. Final hearing level was 52.7 \pm 29.1 dB in the steroids group, 47.0 \pm 27.7 dB in the steroids + PGs groups, 48.7 \pm 25.9 dB in the ITS group, and 57.2 \pm 29.5 dB in the no steroids group. The final hearing level of the steroids + PGs group was better than those in the steroids and no steroids groups ($p < .01$). Hearing gain was 33.0 \pm 23.4 dB in the steroids group, 37.8 \pm 23.0 dB in the steroids + PGs group, 35.7 \pm 20.2 dB in the ITS group, and 27.7 \pm 20.4 dB in the no steroids group. The hearing gain in the steroids + PGs group was again higher than those in the steroids and no steroids groups ($p < .01$), and that in the ITS group was higher than that in the no steroids group ($p < .05$). The ratio of good prognosis (complete recovery or marked improvement) was higher in the steroids + PGs group than in the steroids and no steroids groups ($p < .01$).

Discussion

Evaluation of therapy for idiopathic SSNHL is complicated as there is a certain rate of spontaneous improvement, which ranges between 35% and 65% [13,14]. A meta-analysis of various medical treatments, including corticosteroids, showed a slight but not statistically significant improvement with medical therapy compared with a placebo [15]. As there is no high-quality evidence, initial systemic corticosteroid therapy is regarded as an option in the American Clinical Practice Guideline for idiopathic SSNHL [16]. In this survey, hearing gain in the steroids, ITS, and no steroids groups was 33.0 \pm 23.4 dB, 35.7 \pm 20.2 dB, and 27.7 \pm 20.4 dB, respectively. The ratio of good prognosis in the steroids, ITS, and no steroids groups was 60.3%, 62.8%, and

53.8%, respectively. The effect of systemic or intratympanic corticosteroid therapy was slightly better than the effect observed in patients not administered corticosteroids, but this difference was not significant. Lee et al. [17] reported that steroid dose reduction increased the possibility of no recovery. Although the efficacy of corticosteroid therapy for idiopathic SSNHL has been questioned, systemic or intratympanic corticosteroid therapy might still be considered.

In this survey, the use of PGs in combination with corticosteroid administration was associated with good hearing prognosis. PGs have numerous biological actions, such as the inhibition of receptor-mediated stimulation of platelet aggregation, cytoprotection, and vasodilation [18]. Ogawa et al. [10] reported that there were no significant differences between treatment with steroid + PGE₁ and steroid only, although hearing improvement at high frequencies was significantly better in the steroid + PGE₁ group than in the steroid only group. Ahn et al. [19] reported that lipo-PGE₁ may have beneficial effects in the treatment of idiopathic SSNHL in patients with type 2 diabetes. On the other hand, a clinical trial in Japan using a single drug did not show any differences between the PGE₁ only and steroid only groups [20]. In this study, we investigated initial treatment efficacy in idiopathic SSNHL patients with severe hearing loss, and found that the use of PGs appeared to afford better hearing outcomes. We also performed an analysis of the type of patients for whom steroid + PGs had been more effective. In this further analysis, we compared the hearing outcome between the steroids group and steroids + PGs group stratified by gender, side of hearing loss, age group (under 65 or 65 and over), days from onset of hearing loss (under 4 days or 4–7 days), initial grade of hearing loss (3 or 4), presenting symptoms (tinnitus, vertigo), and presenting systemic comorbidities (diabetes mellitus, hyperlipidemia, heart disease, brain infraction). The results revealed that steroids + PGs were more effective in patients who were female, aged 65 and over, treated under 4 days from the onset of hearing loss, and presenting with vertigo, based on our definition of effective as a calculated odds ratio of over 1.50 (see Supplemental Table 1).

There were various biases in this survey. This study was retrospective, and we excluded patients who had received ITS for salvage therapy in order to ascertain the effectiveness of the initial treatment for idiopathic SSNHL. In fact, 89 patients from the steroids group (accounting for 10.1% of the patients receiving systemic steroids without PGs as the initial therapy) and 73 patients from the steroids + PGs group (16.3% of the patients receiving systemic steroids + PGs as the initial therapy) were excluded for that reason. Therefore, there is a possibility that the hearing prognoses for the steroids and steroids + PGs groups might be better than the actual results. However, as the hearing outcome was better in the steroids + PGs group than in the steroids group, the effectiveness of PGs combined with steroid appears certain. In addition, age and the frequency of diabetes were higher in the ITS and no steroids groups. In this study, we did not find any relationship between hearing outcome and patient characteristics, including age and diabetes. Although further prospective randomized clinical

studies are necessary to fully evaluate the usefulness of initial therapies, we believe that the use of PGs in combination with systemic corticosteroid therapy is associated with a good hearing prognosis in patients with severe idiopathic SSNHL.

Conclusions

A large number of patients with idiopathic SSNHL were registered in a multicenter database, and the relationship between initial treatment type and hearing outcome was analyzed. The effect of systemic or intratympanic corticosteroid therapy was slightly better than that of therapy without corticosteroids, but the difference was not significant. The use of PGs in combination with steroid administration was associated with good hearing prognosis in idiopathic SSNHL patients with severe hearing loss.

Acknowledgements

This study was supported by a Health and Labour Sciences Research Grant for Comprehensive Research on Disability Health and Welfare from the Ministry of Health, Labour and Welfare, Japan (<http://www.mhlw.go.jp/english/>) (S.U.).

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding

This study was supported by a Health and Labour Sciences Research Grant for Comprehensive Research on Disability Health and Welfare from the Ministry of Health, Labour and Welfare, Japan (<http://www.mhlw.go.jp/english/>) (S.U.).

References

- [1] Nakashima T, Sato H, Gyo K, et al. Idiopathic sudden sensorineural hearing loss in Japan. *Acta Otolaryngol.* 2014;134:1158–1163.
- [2] Fetterman BL, Saunders JE, Luxford WM. Prognosis and treatment of sudden sensorineural hearing loss. *Am J Otol.* 1996;17:529–536.
- [3] Suckfüll M, Wimmer C, Reichel O, et al. Hyperfibrinogenemia as a risk factor for sudden hearing loss. *Otol Neurotol.* 2002;23:309–311.
- [4] Norris CH. Drugs affecting the inner ear: a review of their clinical efficacy, mechanisms of action, toxicity, and place in therapy. *Drugs.* 1988;36:754–772.
- [5] McCall AA, Swan EE, Borenstein JT, et al. Drug delivery for treatment of inner ear disease: current state of knowledge. *Ear Hear.* 2010;31:156–165.
- [6] Wei BP, Mubiru S, O'Leary S. Steroids for idiopathic sudden sensorineural hearing loss. *Cochrane Database Syst Rev.* 2006;CD003998.
- [7] Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: I. A systematic review. *Arch Otolaryngol Head Neck Surg.* 2007;133:573–581.
- [8] Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: II. A meta-analysis. *Arch Otolaryngol Head Neck Surg.* 2007;133:582–586.
- [9] Nakashima T, Kuno K, Yanagita N. Evaluation of prostaglandin E1 therapy for sudden deafness. *Laryngoscope.* 1989;99:542–546.
- [10] Ogawa K, Takei S, Inoue Y, et al. Effect of prostaglandin E1 on idiopathic sudden sensorineural hearing loss: a double-blinded clinical study. *Otol Neurotol.* 2002;23:665–668.
- [11] Lee HY, Kim JC, Choi MS, et al. Therapeutic effect of combined steroid-lipoprostaglandin E1 for sudden hearing loss: a propensity score-matched analysis. *Am J Otolaryngol.* 2015;36:52–56.
- [12] Agarwal L, Pothier DD. Vasodilators and vasoactive substances for idiopathic sudden sensorineural hearing loss. *Cochrane Database Syst Rev.* 2009;CD003422.
- [13] Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. *Arch Otolaryngol.* 1980;106:772–776.
- [14] Mattox DE, Simmons FB. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol.* 1977;86:463–480.
- [15] Labus J, Stützer H, Michel O. Meta-analysis for the effect of medical therapy vs. placebo on recovery of idiopathic sudden hearing loss. *Laryngoscope.* 2010;120:1863–1871.
- [16] Stachler RJ, Chandrasekhar SS, Archer SM, et al. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg.* 2012;146:S1–S35.
- [17] Lee HY, Kim DK, Park YH, et al. Prognostic factors for profound sudden idiopathic sensorineural hearing loss: a multicenter retrospective study. *Eur Arch Otorhinolaryngol.* 2017;274:143–149.
- [18] Karetova D, Bultas J, Vondracek V, et al. Alprostadil: modes of actions in peripheral arterial occlusive disease. *Am J Ther.* 1997;4:359–363.
- [19] Ahn JH, Kim TY, Kim YJ, et al. Lipo-prostaglandin E1 in combination with steroid therapy is effective for treatment of sudden sensorineural hearing loss in Korean patients with Type 2 diabetes. *Diabet Med.* 2006;23:1339–1343.
- [20] Kanzaki J, Inoue Y, Ogawa K, et al. Effect of single-drug treatment on idiopathic sudden sensorineural hearing loss. *Auris Nasus Larynx.* 2003;30:123–127.