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Prognostic impact of salvage treatment on hearing recovery in patients with sudden sensorineural hearing loss refractory to systemic corticosteroids: A retrospective observational study

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ABSTRACT

Objective: To determine the prognostic factors for hearing recovery in patients with sudden sensorineural hearing loss (SSHL) refractory to systemic corticosteroids following salvage treatment.

Methods: This is a retrospective observational study at nine tertiary referral hospitals. A total of 120 patients with sudden deafness refractory to systemic corticosteroids were enrolled. The patients were randomly assigned to receive topical application of recombinant human IGF-1 or intratympanic injection of dexamethasone as salvage treatment. Multiple regression analysis was performed to identify determinants of hearing recovery using pure tone audiometry results at 8 weeks after treatment. Clinical predictors that were evaluated included age, sex, pretreatment hearing level, presence of vertiginous symptoms, days to study entry from symptom onset and salvage treatment assignment (IGF-1 vs. dexamethasone).

Results: The linear regression model identified age ($P = 0.001$), pretreatment hearing level ($P < 0.001$), days to study entry from symptom onset ($P = 0.011$) and treatment assignment ($P = 0.033$) at 8 weeks after treatment as significant variables influencing the recovery of pure tone

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audiometry average thresholds. Younger age (<60 years), early initiation of salvage treatment and treatment with topical IGF-1 therapy had significant effects on hearing recovery.
Conclusion: The results indicate that early initiation and choice of treatment modalities for salvage treatment may be important for the prognosis of patients with refractory SSHL. The positive effect of topical IGF-1 therapy on hearing recovery indicates its utility as salvage treatment.

1. Introduction

Sudden sensorineural hearing loss (SSHL), an unexplained unilateral hearing loss over <72 h, is a common cause of acute-onset hearing impairment. The incidence of SSHL is reportedly 5–20/100,000 persons per year [1]. Approximately 35,000 patients with SSHL consult a doctor each year in Japan [2]. The standard treatment for SSHL has been systemic corticosteroid treatment [3,4]. A recent study has demonstrated that intratympanic injection of corticosteroids is not inferior in hearing recovery as an initial treatment to systemic corticosteroids [5]. However, according to the guidelines of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [6], initial corticosteroid treatment is ranked as an 'Option' for SSHL, indicating that the quality of evidence supporting its use is questionable or that well-controlled studies have demonstrated little advantage of one approach over another. One reason for poor evidence regarding the efficacy of initial corticosteroid use may be the high incidence of spontaneous hearing recovery in patients with SSHL [7–9], which occurs in 30%–60% of patients. Hyperbaric oxygen therapy is also considered as an 'Option'. On the other hand, as salvage treatment, intratympanic injection of corticosteroids is included as a 'Recommendation', meaning that the benefits exceed the risks; however, evidence for this is also lacking [6]. Apart from these options, no other therapeutic approaches are recommended for the treatment of SSHL in the AAO-HNS guidelines [6].

To provide a new therapeutic option for SSHL, we developed a topical insulin-like growth factor-1 (IGF-1) therapy in which gelatin hydrogels impregnated with recombinant human IGF-1 are applied to the middle ear. IGF-1 is a polypeptide hormone with endocrine, paracrine and autocrine effects. It plays roles in both embryological and postnatal development, contributes to growth and is involved in the maintenance and protection of various organs, including the cochlea [10,11]. In animal experiments, IGF-1 provided protective effects for cochlear hair cells against toxicity [12], noise trauma [13,14] and ischaemia [15]. Based on these findings, we previously performed a single-armed, prospective clinical trial of topical IGF-1 therapy in patients with SSHL refractory to systemic corticosteroids, which demonstrated the safety of this therapy and suggested the efficacy as salvage treatment [16]. Recently, to test the efficacy of topical IGF-1 therapy as salvage treatment for SSHL, a randomised controlled trial of topical IGF-1 therapy for SSHL refractory to systemic corticosteroids was performed [17]. In that trial, an intratympanic corticosteroid was used as a control treatment. Topical IGF-1 therapy elicited better hearing recovery than an intratympanic corticosteroid in patients with SSHL refractory to systemic corticosteroids, with higher safety [17].

In this study, to examine the prognostic impact of salvage treatment on hearing recovery in patients with SSHL refractory to systemic corticosteroids, we performed multiple regression analyses of potential prognostic factors for hearing recovery as assessed by pure tone audiometry (PTA) in subjects from our randomised controlled trial. Patient's age, sex, pretreatment hearing level, presence of vertiginous symptoms, days to study entry from symptom onset and treatment assignment were evaluated as clinically plausible predictors of recovery.

2. Materials and methods

2.1. Study design and setting

This was a retrospective observational study of subjects who had been enrolled in a multicentre, randomised, open, parallel-group clinical trial of topical IGF-1 therapy for SSHL refractory to systemic corticosteroid treatment (UMIN Clinical Trials Registry Number UMIN000004366) [17]. This trial was conducted from November 2010 through October 2013 at nine tertiary referral hospitals in Japan (Kyoto University Hospital, Hirosaki University Hospital, University of Tsukuba Hospital, Toranomon Hospital, Shinshu University Hospital, Nagoya City University Hospital, Kobe City Medical Center General Hospital, Ehime University Hospital and Kyushu University Hospital).

2.2. Ethical considerations

The study protocol, manual of procedures and informed consent form were approved by the institutional review boards of all participating sites (Ethical Committee of the Graduate School of Medicine, Kyoto University [C470], Ethical Committee of the Graduate School of Medicine, Hirosaki University [2011-145], Ethical Committee of University of Tsukuba Hospital [H23-13], Ethical Committee of Toranomon Hospital [2011-4-15], Ethical Committee of Shinshu University Hospital [1705], Ethical Committee of Nagoya City University Hospital [45-11-0005], Ethical Committee of Kobe City Medical Center General Hospital [1], Ethical Committee of Ehime University Hospital [1105003] and Ethical Committee of the Graduate School of Medicine, Kyushu University [23011]). All patients had given written informed consent.

2.3. Subjects

The subjects comprised 120 patients aged ≥20 years who had been diagnosed with SSHL within 25 days of onset and