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Intratympanic dexamethasone as initial therapy for idiopathic sudden sensorineural hearing loss: Clinical evaluation and laboratory investigation

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Abstract

Objective: To evaluate the effect of intratympanic dexamethasone (ITD) as initial therapy for idiopathic sudden sensorineural hearing loss (ISSHL) as well as to determine the concentration-dependent time course distribution of dexamethasone in the inner ear.
Methods: Sixty-six patients with profound ISSHL were included. Twenty-two were treated with ITD and the rest as control. Audiograms were performed before the treatment and one month afterwards. In the animal study, dexamethasone of different concentrations (5, 10 and 20 mg/ml) was injected into the tympanums of three groups of SD rats (Groups A, B and C), their inner ears dissected free at various postinjection survival intervals. Immunofluorescence was applied to detect the locations of dexamethasone.
Results: The overall rate of good prognosis was 77.27% in ITD group, which was not significantly different from 81.82% in the control group. In the animal study, the higher local concentration and longer lasting period was found in Groups B and C.
Conclusions: ITD at 5 mg/ml did not add effect to systemic steroids in improving hearing outcomes in patients with ISSHL. An increase in dexamethasone concentration led to large variations in pharmacokinetics in animal study, showing potential value in optimizing the drug delivery protocols and improving the therapeutic results.

Keywords: Dexamethasone; Inner ear; Tissue distribution; Sudden sensorineural hearing loss

Clinical use of intratympanic perfusion with steroids began when Sakata used it for Meniere's disease, reporting clinical benefits to the patients with no obvious side effects. And ten years later, Silverstein began to introduce the new administration route to the treatment of sudden deafness.

Over the past 15 years, office-based intratympanic steroids treatment for idiopathic sudden sensorineural hearing loss (ISSHL) has increased, yet remained controversial. Clinically, intratympanic dexamethasone (ITD) is applied in three main protocols for the treatment of ISSHL: these are initial treatment without systemic steroids, adjunctive treatment given concomitantly with systemic steroids, and salvage therapy after failure of systemic steroids. Most of the studies are the last type [1–4], while only several of them the first one. In 2004, Doyle reviewed the literature regarding the use of intratympanic steroids in the treatment of ISSHL and found there were few controlled prospective studies, concluding from the published studies that a weak recommendation was made to use intratympanic steroids in treating ISSHL when oral steroid failed or was contradicted [5]. In 2008, Hamid reported the inconsistence of the clinical effects of ITD partly due to concentration variations, i.e. the doses ranging considerably from 4 to 24 mg/ml for dexamethasone [6].

Many animal experiments paved the way for the clinical use of ITD. First of all, round window membrane was proved to be semi-permeable, and also the major entry site for intratympanic agents into the inner ear scala tympani. This

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fact served as an important basis for the new administration route. Furthermore, Chandrasekhar demonstrated that dexamethasone delivered intratympanically resulted in higher perilymph steroid levels than when delivered systemically [7]. Several other experiments also suggested otoprotective effects of ITD in noise-induced hearing loss and ototoxity [8]. Dexamethasone was believed to affect levels of various metabolic enzymes and cellular proteins [8–10]. However, most of the studies focused on the drug's concentrations in perilymph and endolymph after ITD [11,12]. The important issues that have so far received little consideration were:

(1) What parts of the inner ear does dexamethasone reach and exert its influence, in what concentration and with what time course?
(2) Does a higher concentration result in a greater absorption and a longer lasting period?

The purpose of the study was firstly to evaluate the clinical effect of ITD as an initial therapy for ISSHL, secondly to conduct an investigation into the concentration-dependent pharmacokinetics of dexamethasone in the inner ears after ITD for the purpose of improving the understanding and usage of the drug.

1. Materials and methods

1.1. Clinical study

The prospective controlled clinical trial involved 66 patients diagnosed with profound ISSHL between May 2007 and February 2008 in the Department of Otolaryngology, EYE & ENT Hospital of Fudan University. The subjects met all the following criteria: (1) no contraindications for general steroids use; (2) within 2 weeks after the onset; (3) no history of previous treatment; (4) the average threshold of pure tone audiogram (PTA) (250–4000 Hz) over 90 dB. The study protocol was approved by the Institutional Board of EYE & ENT Hospital and in accordance with the Helsinki Declaration, and a written informed consent, obtained from each patient.

All the patients were treated with a 9-day course of intravenous steroids, initial dosage of dexamethasone, 15 mg, and every 5 mg reduced every 3 days. A continuous infusion containing 10 μg Prostaglandin E1 was also administered intravenously for 7 days along with a 30-day hyperbaric oxygen therapy (hyperbaric oxygen administered with 2.2 ATA for 60 min daily for 30 consecutive days). The subjects were divided into two groups according to their choices after introducing ITD to them. Those who had chosen the ITD group received an additional dosage of 0.8 ml of dexamethasone (5 mg/ml) every other day transtympanically for 5 times. Audiograms were performed before the treatment and one month afterwards, and

Table 1
Criteria for hearing improvement in ISSHL.

Level of improvement	Criteria
Cured	1. All five frequencies within normal level, or 2. Back to the same hearing level before SSHNL episode, or 3. Back to the same level as the other ear
Marked recovery	The improvement of the average hearing level of the five frequencies >30 dB
Slight recovery	The improvement of the average hearing level of the five frequencies >10 dB but ≤30 dB
Unchanged	The improvement of the average hearing level of the five frequencies ≤10 dB

Established in 1973 by the Sudden Deafness Research Committee of the Ministry of Health and Welfare, Japan. ISSHL: idiopathic sudden sensorineural hearing los.

improvement in hearing was categorized into 4 grades (Table 1), with the grades of ''cured'' and ''marked recovery'' considered as good prognosis, and of ''slight recovery'' and ''unchanged'' as poor.

All values were expressed as mean ± SD, and stata 8.0 was used for statistics with $p < 0.05$ defined as the cut off for statistical significance.

1.2. Animal study

In our study, 144 adult SD rats, weighed 200–250 g, with a normal preyer reflex, were used to determine the transport of dexamethasone from the middle ear to the inner ear and its distribution there. The animals were anesthetized with a ketamine–xylazine cocktail, their eardrums observed under a surgical stereomicroscope. Dexamethasone of different concentrations at 5 mg/ml, 10 mg/ml and 20 mg/ml (Sigma, D1159, USA) was injected (40 μl) into the tympanums of 3 groups of SD rats, named Groups A, B and C respectively. The distributions in the inner ears were measured at various survival intervals of 5, 10, 15, and 30 min; 1, 2, 4, 8, and 12 h; and 1, 2 and 3 days, in each group of which the same was done with four rats at each survival interval. And four slides near the cochlear axis were selected at random in each rat for grey value analysis. The controls of the opposite ear were injected with phosphate-buffered saline.

After injection, the rats were anesthetized and sacrificed at various survival intervals, with the inner ears dissected free of the skull and fixed with 4% paraformaldehyde overnight. With 5–7 days of decalcification in 10% ethylenediamine tetra-acetic acid, the tissues were cryostat sectioned and placed on slides for immunofluorescence.

To detect the distributions of dexamethasone, rabbit antibodies (AbD Serotec, Britain) to the drug (anti-dexamethasone) were applied, followed by anti-rabbit second antibody conjugated with cy3 (Sigma, USA) [13]. Those treated as controls served as negative ones.