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Evaluation of intratympanic dexamethasone for treatment of refractory sudden sensorineural hearing loss

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Abstract: Objective: To observe and compare the efficacy of intratympanic application of dexamethasone (DXM) for the treatment of refractory sudden sensorineural hearing loss (SSNHL), the DXM was given in three different ways: by tympanic membrane injection, by drip through a ventilation tube, and by perfusion through a round window catheter. Methods: We conducted a nonrandomized retrospective clinical trial involving 55 patients with refractory SSNHL. For 21 patients (the perfusion group), DXM (2.5 mg/0.5 ml) was perfused transtympanically through a round window catheter using an infusion pump for 1 h twice a day for 7 d giving a total amount of 35.0 mg. For 23 patients (the injection group), DXM (2.5 mg/time) was injected by tympanic membrane puncture at intervals of 2 d on a total of four occasions giving a total amount of 10.0 mg. For 11 patients (the drip group), DXM (2.5 mg/0.5 ml) was dripped via a ventilation tube placed by myringotomy, once on the first day and twice a day for the remaining 6 d giving a total amount of 32.5 mg. Thirty-two patients with refractory SSNHL who refused to undertake further treatments were defined as the control group. Hearing recovery and complications were compared among the groups. Hearing results were evaluated based on a four-frequency (0.5, 1.0, 2.0, 4.0 kHz) pure tone average (PTA). Results: Post-treatment audiograms were obtained one month after treatments were completed. The improvements in average PTA for the perfusion, injection, and drip groups were 9.0, 8.6, and 1.7 dB, respectively. Hearing improvement was significantly greater in the perfusion and injection groups than in the control group (1.4 dB) (P<0.05). In the perfusion group, 8 out of 21 patients (38.1%) had a PTA improvement of 15–56 dB (mean 29.8 dB); in the injection group, 8 out of 23 patients (34.8%) had a PTA improvement of 16–54 dB (mean 24.9 dB); in the drip group, 1 of 11 patients (9.1%) had a PTA improvement of 26.0 dB; in the control group, 3 out of 32 patients (9.4%) had a PTA improvement of 15–36 dB (mean 14.9 dB). Conclusions: Topical intratympanic application of DXM is a safe and effective method for the treatment of SSNHL cases that are refractory to conventional therapies.

Key words: Sudden sensorineural hearing loss, Dexamethasone, Intratympanic, Round window
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1 Introduction

Sudden sensorineural hearing loss (SSNHL) is a common otologic emergency, presenting mostly as an acute unilateral deafness, with an abrupt onset (generally within 3 d), of more than 30 dB hearing loss at three consecutive frequencies. Many causes of SSNHL have been hypothesized including viral infection of the labyrinth or cochlear nerve, vascular incident, perilymphatic hypoxia, labyrinthine membrane rupture, and inflammatory and autoimmune disorders (Fetterman *et al*., 1996; Hughes *et al.*, 1996). The etiology and pathogenesis of SSNHL are still unclear, and its treatment remains controversial. The effectiveness of all treatments is about 65% at present. For many years, corticosteroids have been used to treat a variety of inner ear disorders. Recently, a number of reports have suggested that transtympanic steroid perfusion offers many obvious advantages

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over gastrointestinal or intravenous steroid delivery to treat inner ear disease. The theoretical advantages of transtympanic steroid delivery include: (1) a higher concentration of steroid can be delivered to the inner ear compared to other routes of delivery; (2) systemic side effects of steroid use can be avoided (Barrs, 2004; Dodson and Sismanis, 2004; Rauch, 2004).

Dexamethasone (DXM) can be applied intratympanically in different ways. In this study, we observed and compared the efficacies of different methods of intratympanic application of DXM for the treatment of SSNHL which does not respond to the conventional therapies, including the administration of a vascular dilator, anti-coagulator, neural nutrients or hyperbaric oxygen therapy. The three different methods were: perfusion via a round window catheter, tympanic membrane injection, and drip through a ventilation tube.

2 Materials and methods

2.1 Clinical materials

Institutional Review Board approval was obtained before proceeding with the study. Between July 2003 and December 2006, at the Department of Otorhinolaryngology in the Second Xiangya Hospital, we retrospectively reviewed 313 SSNHL patients who met diagnosis criteria proposed by the Chinese Otorhinolaryngology Association in Shanghai in 1996. One hundred and twenty-seven SSNHL patients who had shown no response to conventional therapies were defined as refractory SSNHL cases. Among them, 21 patients who underwent DXM perfusion treatment through a round window catheter fed by an infusion-pump were defined as the perfusion group; 23 patients who received DXM by injection through a tympanic membrane puncture were defined as the injection group; 11 patients who received DXM via a drip through a ventilation tube placed by myringotomy were defined as the drip group; another 32 patients who rejected further treatments were followed as a control group; the remaining 40 patients without complete clinical records were excluded. The clinical features of the subjects are summarized in Table 1. There were no significant differences among groups (P>0.05) in age, the course of disease on admission, hospitalization time, average pure tone average (PTA) on admission, or average PTA after conventional treatments for 2–5 weeks (4.3 weeks on average). Conventional treatments included the administration of a vascular dilator, anti-coagulator, neural nutrients or hyperbaric oxygen therapy, and intravenous DXM injections. Intravenous DXM injections (10 mg once daily (q.d.) for 3 d, followed by a gradually decreasing dose) had been given to 29 patients who had no DXM contraindications (9 cases in the perfusion group, 7 in the injection group, 5 in the drip group, and 8 in the control group).

Table 1 Comparison of pretreatment data of subjects treated in this study

Group	Age (year)	Gender	PTA_a (dB)	PTA_c (dB)
Perfusion (n=21)	47.8±11.3*	13/8#	72±24.2	71±25.2
Injection (n=23)	46.2±13.3	15/8	75±19.2	71±24.2
Drip (n=11)	45.2±13.7	7/4	71±21.2	70±18.1
Control (n=32)	47.7±14.1	17/15	72±21.3	68±21.7

* Data are expressed as mean±standard deviation (SD); # Male/female. PTA_a: average PTA on admission; PTA_c: average PTA after conventional treatment

2.2 DXM perfusion through a round window catheter

The patient was given a local anesthesia with 0.02 g/ml lidocaine and an incision for tympanic exploration was made to form a tympanomeatal flap. This flap was bigger than the one formed by a conventional approach in order to adequately expose the round window niche. For patients whose round window niche cannot be exposed easily, some bone of the infra-posterior external canal wall should be removed with a diamond drill or a curette. Membrane adhesions in the niche were removed using a small hook, and then a piece of gel foam soaked with 5 mg/ml DXM was placed in the niche to fit the niche tightly. A catheter with an inner diameter of 1.5 mm was then introduced through the space between the tympanomeatal flap and the bony wall into the tympanic cavity. The catheter was carefully placed to make contact with the gel foam in the niche. The tympanomeatal flap was then replaced and secured with gel foam. The catheter was fixed by suturing it to the pinna, and then antibiotic-soaked packing was placed in the external canal. Finally, the catheter was attached

to an infusion pump (B. Braun Melsungen AG, Germany). After the operation, 0.5 ml DXM (5 mg/ml) was injected immediately through the catheter, and the patient was advised to remain supine for 30 min with their head turned to the side and the injected ear upright, and to swallow as little as possible to keep the DXM in the tympanic cavity. Then 0.5 ml DXM (5 mg/ml) was perfused transtympanically through the round window catheter placed by infusion pump for 1 h twice a day for 7 d, with a total dose of 35.0 mg. The catheter was removed after 7 d of treatment.

2.3 DXM injection through a tympanic membrane puncture

The patients lay on their back and turned their head to one side. After skin disinfection of the external auditory canal, a small cotton ball with 0.05 g/ml phenol glycerin-lidocaine was placed on the tympanic membrane for 3 min. Under an otological microscope, a puncture was made in the posterior-inferior quadrant using a 1-ml syringe, then 0.5 ml of 5 mg/ml DXM was injected gradually over 5 min. This procedure was carried out four times, once every two days, with a total DXM dose of 10.0 mg.

2.4 DXM drip through a tympanic membrane tube

Under local anaesthesia and using an otological microscope, an incision was made in the posterior-inferior quadrant, and a middle-size silicone ventilation tube was fed through it. A total of 0.5 ml of 5 mg/ml DXM was injected gradually through the ventilation tube using a 1-ml syringe for 5 min. The treated ear was kept upright and supine for 30 min. The procedure was carried out once a day for 7 d with a total DXM dose of 32.5 mg. To protect the middle ear from infection, 5 mg/ml chloromycetin eyedrops were applied once a day.

During the course of treatment, subjective changes in the patients' hearing, tinnitus, vertigo, tympanic membrane perforation, and middle ear infection were observed. One month after the procedure had finished, the hearing results were evaluated based on the PTA of the four frequencies: 0.5, 1.0, 2.0, and 4.0 kHz. Therapeutic efficacy was evaluated according to the criteria of hearing improvement proposed by the Chinese Otorhinolaryngology Association and the Editorial Committee of the Chinese Otorhinolaryngology Journal. A significant hearing improvement was defined as a decrease in PTA of 25 dB or more, and a partial hearing recovery as a decrease of 15 dB or more.

2.5 Statistical analysis

Means±standard deviations (SDs) were calculated and the results were analyzed using SPSS 10.0 software. A comparison between sample means was performed using a *t*-test, and a comparison between sample rates was performed using a χ^2-test.

3 Results

The average PTAs of the perfusion and injection groups showed significant ($P<0.05$) improvements of 9.0 and 8.6 dB, respectively, compared with the control group which showed an improvement of only about 1.4 dB (Table 2). The average PTA improvement of the drip group was 1.7 dB, which was not significantly different from that of the control group ($P>0.05$). In the perfusion group, 8 patients (38.1%) showed hearing improvements of from 15 to 56 dB (about 29.8 dB on average), and 13 patients showed no improvement. In the injection group, 8 patients (34.8%) showed hearing improvements of from 16 to 54 dB (about 24.9 dB on average), and 15 patients showed no improvement. In the drip group, 1 patient (9.1%) showed a hearing improvement of about 26.0 dB, and 10 patients showed no improvement. In the control group, 3 patients (9.4%) showed a hearing improvement of from 15 to 36 dB (about 14.9 dB on

Table 2 Comparison of improvement in pure tone average (PTA) between groups following dexamethasone (DXM) treatment

Group	PTA_c (dB)	PTA_{DXM} (dB)	n_1	n_2
Perfusion (n=21)	71±25.2*	62±21.7	9 (42.9%)	8 (38.1%)
Injection (n=23)	71±24.2	61±18.7	11 (47.8%)	8 (34.8%)
Drip (n=11)	70±18.1	69±17.3	3 (27.3%)	1 (9.1%)
Control (n=32)	68±21.7	66±23.7	7 (21.9%)	3 (9.4%)

*Data are expressed as mean±SD. PTA_c: average PTA after conventional treatment; PTA_{DXM}: average PTA after transtympanic DXM treatment; n_1: number with subjective improvement; n_2: number with improvement

average), and 29 patients showed no improvement. No tinnitus, vertigo, dizziness, or middle ear infections were observed in any patients during the course of treatment. However, in two cases in the perfusion group, the round window catheter had to be reset after a prolapse. Two patients in the drip group suffered tympanic membrane perforation. No other complications were found.

4 Discussion

SSNHL, a common otologic emergency, has a tendency to show spontaneous hearing improvement, but all reports describing treatments indicate that early initiation of treatment will undoubtedly lead to improved prognoses. Because the etiology of SSNHL is not fully understood, there is no universal treatment modality. Success of treatment of any disorder depends on a full understanding of the underlying pathophysiological characteristics. For SSNHL cases with definite causative factors, treatments according to the etiology are very effective. Such treatments include stopping ototoxic medication, treating perilymph fistula and immune inner ear disease, recompressing in cases of inner ear decompression sickness, administering acyclovir for herpes virus or antibiotics for bacterial infection, and correcting metabolic imbalance. For cases without definite causative factors, the therapy for SSNHL is controversial. The most common methods are to improve microcirculation and to increase the blood oxygen concentration according to postulated causative factors such as dysfunction of microcirculation and viral infection (Hughes *et al.*, 1996). Although many medications for treating SSNHL are questionable, the use of corticoids is effective in treating the inflammatory process within the inner ear which might arise from viral infection, an autoimmune disease, or even as a sequel to autolytic changes surrounding an area of ischemia or infarction (Chen *et al*., 2003; Zadeh *et al*., 2003; Jeyakumar *et al*., 2006). The first randomized controlled trial of SSNHL therapy was performed by Wilson *et al*. (1980). They investigated therapeutic efficacy in a study of 67 patients with SSNHL at two clinical sites who were given either corticoid steroid or a placebo. The results showed that overall 61% of the steroid group showed a hearing improvement, compared with 32% of the placebo group. Furthermore, there was a strong correlation between the pretreatment audiogram and the results. Patients with thresholds of 40 dB or less or with mid-frequency losses of up to 85 dB invariably had excellent hearing recovery regardless of which treatment they were assigned.

Recently, a number of uncontrolled case series have reported that transtympanic steroid delivery can achieve a significant hearing improvement rate in patients with SSNHL who have failed to recover with primary oral steroid therapy (Banerjee and Parnes, 2005; Herr and Marzo, 2005; Choung *et al*., 2006; Roebuck and Chang, 2006; Haynes *et al*., 2007). Parnes *et al.* (1999) reported a two-part study in which they used a guinea pig model to compare the concentrations of hydrocortisone, DXM, and methylprednisolone in plasma, endolymph, perilymph, and cerebrospinal fluid when administered by oral, intravenous, or transtympanic routes. The concentration of steroid was highest in endolymph and perilymph following use of the transtympanic route; methylprednisolone produced the highest concentration within the inner ear fluid for the longest time. They went on to inject transtympanically, either DXM or methylprednisolone to 12 patients with SSNHL. Of 12 patients, 3 (25%) showed a full hearing recovery, 3 (25%) showed a partial recovery, and 6 (50%) showed no change. Kopke *et al.* (2001) treated four patients with SSNHL, who had shown no response to oral prednisone, by injection of prednisone through a microcatheter in the middle ear. Two patients showed complete hearing recovery and the other two partial recovery. Lefebvre and Staecker (2002) placed a tube near the round window and perfused methylprednisolone (62.5 mg/ml) continuously at 10 μl/h for 10 d using a mini-pump in six refractory patients with SSNHL who had received conventional therapy with oral or intravenous steroid injection. The range of hearing threshold of all the patients was improved by from 16.25 to 25.00 dB. Gianoli and Li (2001) administered DXM or methylprednisolone by transtympanic injection to 22 refractory patients who had no response to oral corticoid. Ten patients (44%) showed some degree of improvement.

We adopted the three different therapies mentioned above to treat 55 patients with SSNHL who had shown no response to conventional therapy. The

total effective rate (30.9%) was much higher than that of the control group ($P<0.05$). In our study, the perfusion group showed the most improvement, and the drip group showed no advantage over the other two groups. Therefore we think that perfusion through a round window catheter placed by means of an infusion pump is a better transtympanic delivery technique. Its advantages were: (1) local application of DXM (>5 mg/d) provided a constant flow and a higher concentration of DXM in the inner ear, and avoided side effects caused by systemic use at the same concentration; (2) perfusion avoided the discomfort and inconvenience caused by repeated tympanic punctuation and leakage of DXM through the Eustachian tube, which can lead to lower levels of DXM in the inner ear; (3) the technique is mini-invasive and uncomplicated. All patients tolerated the procedure well and suffered no apparent vertigo, middle ear infection or tympanum perforation. The method provides patients with refractory SSNHL who have shown no response to conventional therapy, another chance of a cure. In the course of treatment, attention should be paid to the following aspects: (1) The use of anti-coagulation drugs or vascular dilators should be stopped three days prior to the operation to avoid severe bleeding which would make the procedure more difficult; (2) DXM should be perfused carefully to avoid the catheter dropping out; (3) prior to DXM perfusion by infusion pump, the air in the catheter should be expelled using a syringe. For medical units with limited surgical capability, we suggest using DXM injection through a tympanic membrane puncture because this method is easier, less traumatic, and more economical and practical. The puncture should be made using an otologic microscope. We do not recommend using a DXM drip through a tympanic ventilation tube, because DXM can suppress the proliferation of fibroblasts, which may affect wound healing and lead to tympanic membrane perforation (the tympanic membrane perforation rate was about 18.2% in the drip group). Also, this method cannot ensure that all the DXM is delivered to the tympanic cavity. There are more and more reports of the use of corticoid injection by transtympanic methods to treat inner ear disease. However, reports describing the treatment of SSNHL by corticoid perfusion through a round window catheter placed using an infusion-pump are still rare. Our study suggested that intratympanic steroid perfusion is effective for the treatment of refractory SSNHL after failure of conventional therapy and has theoretical advantages over repeated tympanic DXM injection (Lu *et al*., 2006; Ren *et al*., 2006). Our sample size was small, and the results may be affected by many factors such as the natural course of recovery of SSNHL, patient age, severity of deafness, gender and possible placebo effects. Further randomized and controlled studies with larger sample sizes are needed.

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