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Original Article

Pentoxifylline versus Steroid Therapy for Idiopathic Sudden Sensorineural Hearing Loss with Diabetes

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OBJECTIVES: To compare the efficacy of pentoxifylline with that of conventional steroid therapy in diabetic patients with idiopathic sudden sensorineural hearing loss (ISSNHL) and to compare blood sugar levels during hospitalization.

MATERIALS and METHODS: Medical charts were retrospectively reviewed for all diabetic patients admitted to one institution for ISSNHL between 2000 and 2015. We analyzed 298 cases; 50 patients received pulse steroid treatment (steroid group) and 248 received intravenous administration of pentoxifylline only (pentoxifylline group). Hearing change was evaluated by comparing the initial hearing tests with follow-up hearing tests for up to 3 months. Blood sugar levels were also compared between the 2 groups.

RESULTS: At 3 months post-treatment, the degree of hearing recovery was similar between the 2 groups. The pure-tone average was improved from baseline by 17.9±21.2 dB in the steroid group and 18.9±20.7 dB in the pentoxifylline group (p=0.776); hearing recovery rates were also similar (40% vs 39.1%; p=0.826). During hospitalization, average fasting blood sugar levels were higher (203.9±92.0 vs 174.4±54.8 mg/dL; p=0.033) and acute hyperglycemia was more common (48.0% vs 33.1%; p=0.044) with steroid versus pentoxifylline treatment.

CONCLUSION: Hearing recovery rates did not significantly differ between steroid and pentoxifylline treatment in diabetic patients with ISSNHL, but pentoxifylline appeared to be associated with better blood sugar control.

KEYWORDS: Idiopathic sudden sensorineural hearing loss, diabetes mellitus, steroid, pentoxifylline, blood glucose

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) has been defined as the acute onset of ≥30 dB sensorineural hearing loss, over at least 3 contiguous frequencies, occurring within 72 hours [1]. As many as 85%-90% cases are idiopathic, with no known precipitating cause at presentation. Another 10%-15% cases are due to identifiable causes such as autoimmune disease, Meniere's disease, syphilis, and perilymphatic fistula [2]. The incidence of idiopathic sudden sensorineural hearing loss (ISSNHL) has been estimated to range between 5 and 20 cases per 100,000 persons per year [3].

Evidence-based clinical practice guidelines recommend corticosteroids as the initial therapy for ISSNHL [3]. However, although steroids, including intravenous (IV) pulse therapy or oral prednisolone, are commonly prescribed to treat ISSNHL, a recent Cochrane review of the evidence from randomized controlled trials reported that there is no consensus on their effectiveness [4, 5].

A previous investigation of the efficacy of steroidal therapy in diabetic patients with ISSNHL highlights the importance of close monitoring of blood sugar levels during treatment period and the need of more frequent use of insulin [6]. The study found that 67% of the patients treated with IV dexamethasone improved by >10 dB in the pure-tone audiogram, whereas hyperglycemia worsened in 4 patients despite insulin treatment. Another study compared the effectiveness of intratympanic (IT) dexamethasone injection with that of systemic corticosteroids (IV prednisolone followed by an oral prednisolone taper or oral prednisolone only for 10 days), as per schedule, in SSNHL patients with diabetes mellitus (DM) [7]. It reported that all groups experienced significant improvements in hearing gain and recovery rates. However, systemic steroid therapy was discontinued for 1 patient in the oral prednisolone group and 2 patients in the intraveneous group because of poor-controlled hyperglecemia. In contrast, none of the patients in the IT group developed this complication.

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Steroids are known to intensify hyperglycemia in patients with a history of DM and also lead to DM in those without any history of hyperglycemia [8]. In some cases, steroids trigger acute complications such as diabetic ketoacidosis and hyperosmolar hyperglycemic state [9].

Cochlear ischemia has been considered to be a potential etiology of SSNHL. Therefore, vasoactive agents, such as *Ginkgo biloba* extract, dextran, and pentoxifylline, have been used with an aim to gain more blood flow in the cochlea [10, 11]. Pentoxifylline has been reported to have an ability of increasing erythrocyte flexibility, reducing blood viscosity, and increasing microcirculatory flow [12, 13].

DM can cause microvascular injuries and other microcirculatory disorders including unexpected increment of blood viscosity and thrombotic and embolic events [14]. Notably, the prevalence of DM in adults has increased from 4.7% in 1980 to 8.5% in 2014 [15]. This increase in DM prevalence warrants careful assessment of treatment outcomes and close monitoring of any treatment-related complications of ISSNHL in diabetic patients.

The aim of this retrospective study was to evaluate the efficacy of pentoxifylline with that of conventional corticosteroid therapy in diabetic patients with ISSNHL and to monitor their blood sugar control during hospitalization.

Table 1. Inclusion criteria

≥18 years old
Acute onset of ≥30 dB unilateral sensorineural hearing loss, over at least 3 contiguous frequencies, occurring within 72 hours
No identifiable cause for the hearing impairment†
Not recurrent sudden hearing loss
No other neurological signs (except for dizziness, vertigo, and tinnitus)
Availability of pre-treatment and post-treatment audiograms up to 3 months
Have a history of DM with medication control (either OHA or Insulin therapy)

†Meniere's disease, cochlear trauma, autoimmune disease, syphilis, Lyme disease, ototoxic drug, and perilymphatic fistula
DM: diabetes mellitus; OHA: oral hypoglycemic agent

MATERIALS and METHODS

Medical charts were retrospectively reviewed for all diabetic patients admitted for ISSNHL to a single tertiary hospital between 2000 and 2015. A total of 298 patients were included in this study according to the inclusion criteria presented in Table 1.

Patients with an identified etiology, recurrent hearing loss, bilateral hearing loss, newly diagnosed or uncontrolled diabetes, concomitant middle ear disease, or previous surgery in the affected ear were excluded. Any patients receiving concomitant systemic steroid and pentoxifylline therapy were also excluded. This study was approved by the Institutional Review Board of the China Medical University Hospital. Informed consent is not necessary because of the retrospective nature of this study.

Detailed profiles were constructed for each patient that included demographic data, affected ear, duration from the onset of hearing loss to the beginning of therapy, treatment modalities, comorbidities, regular blood tests, and any associated symptoms (Table 2). Details

Table 2. Demographics, baseline auditory data, and DM-related parameters

	Pentoxifylline group (n=248)	Corticosteroid group (n=50)	p
Mean age (years)	61.4±10.8	59.2±11.1	0.192
Sex: males: females, n (%)	125:123 (50.4:49.6)	25:27 (46:54)	0.570
Affected ear: left:right, n (%)	121:127 (48.8:51.2)	31:19 (62:38)	0.088
Onset to treatment (days)	6.0±7.4	6.6±5.6	0.572
Dizziness or Vertigo, n (%)	126 (50.8)	28 (56.0)	0.503
Pure-tone threshold at each frequency (dB)			
0.25 kHz	68.9±24.9	76.3±23.6	0.057
0.5 kHz	77.5±22.3	81.2±19.0	0.275
1 kHz	81.1±22.2	85.3±18.7	0.221
2 kHz	78.9±23.0	82.7±21.2	0.291
4 kHz	83.7±24.1	85.5±22.1	0.644
8 kHz	88.4±20.9	90.4±17.6	0.501
PTA (dB) of affected ear	80.3±20.7	83.8±18.9	0.297
HbA1c (%)	8.6±2.2	8.7±1.2	0.939
FBS on Day 1 (mg/dL)	220.1±112.6	250.0±98.0	0.082
DM therapy: OHA:insulin, n (%)	191:57 (77:23)	40:10 (80:20)	0.714

DM: diabetes mellitus; PTA: pure-tone threshold average, determined by calculating the mean of the 0.5, 1, 2, and 4 kHz thresholds. HbA1c: glycated hemoglobin; FBS: fasting blood sugar; OHA: oral hypoglycemic agent

Table 3. Hearing gain after treatment for 1 week, 4 weeks, and 12 weeks

	Pentoxifylline group (n=248)				Corticosteroid group (n=50)				
Hearing gain (dB)	**Baseline**	**1 week**	**4 weeks**	**12 weeks**	**Baseline**	**1 week**	**4 weeks**	**12 weeks**	**p**
0.25 kHz	68.9±24.9	8.0±21.4	15.1±26.1	20.8±27.5	76.3±23.6	10.7±22.3	20.1±25.7	22.7±24.9	NS
0.5 kHz	77.5±22.3	8.9±20.4	17.2±24.8	20.6±39.3	81.2±19.0	10.5±17.4	18.6±23.1	25.2±24.3	NS
1 kHz	81.1±22.2	8.4±16.7	16.0±20.7	21.0±22.9	85.3±18.7	10.2±15.3	16.7±23.9	21.5±21.3	NS
2 kHz	78.9±23.0	8.1±15.9	14.1±19.5	17.6±20.6	82.7±21.2	10.9±14.6	15.4±22.1	19.0±19.6	NS
4 kHz	83.7±24.1	5.14±16.9	10.4±19.6	13.8±20.4	85.5±22.1	11.9±17.6*	15.9±21.6	17.8±20.9	p=0.011*
8 kHz	88.4±20.9	2.6±12.8	6.8±15.9	9.5±16.1	90.4±17.6	5.0±12.8	8.9±15.3	7.6±13.5	NS
PTA	80.3±20.7	7.6±15.2	14.4±18.8	18.9±20.7	83.8±18.9	10.8±14.4	16.6±21.0	17.9±21.2	NS

PTA: pure-tone threshold average, determined by calculating the mean of the 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz thresholds. NS: not significant between 2 groups (at 1 week, 4 weeks, and 12 weeks).

*The steroid group had significant hearing gain at 4 kHz 1 week after treatment (p=0.011), but had no significant hearing gain at 4 and 12 weeks after treatment.

such as fasting blood sugar (FBS) levels, types of DM medications used, HbA1c values within the previous 3 months, and any acute complications such as hyperosmolar hyperglycemic state and keto-acidosis were also recorded. Clinical examinations were performed in all patients, and those with identifiable etiologies of hearing loss were excluded.

Patients in the steroid group received IV hydrocortisone (China Chemical & Pharmaceutical Company, Taipei, Taiwan) 300 mg daily on Days 1–3, followed by oral prednisolone 60 mg on Day 4 and 50 mg on Day 5. After discharge on Day 5, the patients commenced oral prednisolone on Day 6 at a dose of 40 mg, which was decreased thereafter by 10 mg daily until a daily maintenance dose of 10 mg continuing up to Day 14. The pentoxifylline group received IV pentoxifylline (Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) 300 mg daily for 5 days, followed by oral pentoxifylline 1200 mg daily for 9 days.

Pure-tone thresholds for air conduction were conducted at 0.25, 0.5, 1, 2, 4, and 8 kHz frequencies. The pure-tone average (PTA) was determined by calculating the mean of the 0.5, 1, 2, and 4 kHz thresholds. Audiometric data were recorded at the time of admission before treatment and at 1, 4, and 12 weeks after treatment initiation.

Hearing change during treatment was assessed by comparing the hearing test results before the treatment with those at 3 months. Pure-tone threshold improvements in each individual tone (0.25, 0.5, 1, 2, 4, and 8 kHz) were recorded. Patients were also categorized into complete, partial, or no recovery of hearing groups according to the definition proposed by the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) Clinical Practice Guidelines: 1) complete recovery, post-treatment PTA return to within 10 dB hearing level of the normal ear; 2) partial recovery, defined in 2 ways: 1. For ears that were nonserviceable (≥50 dB on PTA and ≤50% speech discrimination score) after the onset of hearing loss, return to serviceable hearing will be considered as partial recovery; 2. for ears that were serviceable, a 10 dB improvement in PTA will be considered as partial recovery; and 3) no recovery, post-treatment PTA improvement was <10dB. Hearing level of the normal ear recorded before treatment initiation was used as baseline for calculating hearing recovery.

In both groups, blood sugar control was evaluated by average FBS levels during hospitalization. Acute hyperglycemia during treatment was defined as FBS >300 mg/dL or FBS >200 mg/dL in those with HbA1c values <8% within the 3-month period prior to hospitalization.

Severity of SSNHL was classified as mild, 26–40 dB; moderate, 41-55 dB; moderately severe, 56–70 dB; severe, 71–90 dB; and profound: >90 dB hearing loss [16].

Statistical analysis of the data was performed using the Statistical Packages for the Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA). The independent sample t-test was used for comparing numerical variables, and the Chi-square test was used for categorical variables. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Among the 298 patients in this analysis, 50 were in the steroid group (mean age, 59.2±11.1 years) and 248 patients were in the pentoxifylline group (mean age, 61.4±10.8 years). The male-to-female ratio in the steroid group was 46%: 54%; the male-to-female ratio in the pentoxifylline group was 50.4%:49.6%. The PTA at the time of admission was 83.8±18.9 dB in the steroid group and 80.3±20.7 dB in the pentoxifylline group. The mean baseline HbA1c value was 8.7%±1.2% and the mean FBS was 250.0±98.0 mg/dL in the steroid group; the corresponding values were 8.6%±2.2% and 220.1±112.6 mg/dL, respectively, in the pentoxifylline group. Demographics, baseline auditory data, FBS values on the first day of admission, and HbA1c values for both groups are summarized in Table 2. There were no significant between-group differences prior to treatment.

At 3 months' follow-up, the average hearing gain was 22.7±24.9, 25.2±24.3, 21.5±21.3, 19.0±19.6, 17.8±20.9, and 7.6±13.5 dB, respectively, for audiogram frequencies of 0.25, 0.5, 1, 2, 4, and 8 kHz in the steroid group. The corresponding hearing gain in the pentoxifylline group was 20.8±27.5, 20.6±39.3, 21.0±22.9, 17.6±20.6, 13.8±20.4, and 9.5±16.1 dB, respectively. Average PTA improvements at 12 weeks in the steroid and pentoxifylline groups were 17.9±21.2 and 18.9±20.7 dB, respectively; the between-group difference was not significant (p=0.776). Treatment results at 1, 4, and 12 weeks are shown in Table 3. Hearing improvement at a specific frequency did not significantly differ between the groups

Table 4. Hearing recovery after 3 months†

Recovery	Pentoxifylline group (n=248)	Corticosteroid group (n=50)	p
Complete recovery, n (%)	65 (26.2)	12 (24)	0.826
Partial recovery, n (%)	32 (12.9)	8 (16)	
No recovery, n (%)	151 (60.9)	30 (60)	

†Categorized according to the AAO-HNSF definition supplied in the manuscript.

Table 5. Blood sugar control

	Pentoxifylline group (n=248)	Corticosteroid group (n=50)	p
Average FBS (mg/dL)	174.4±54.8	203.9±92.0	0.033
Acute hyperglycemia†, n (%)	82 (33.1)	24 (48.0)	0.044

FBS: fasting blood sugar

†FBS >300 mg/dL or FBS >200 mg/dL in those with HbA1c <8% within the 3 months prior to hospitalization

except for the significant hearing gain in the steroid group at 4 kHz at 1 week after treatment.

AAO-HNSF values for the steroid group demonstrated a complete recovery rate of 24%, a partial recovery rate of 16%, and a no recovery rate of 60%. The corresponding values for the pentoxifylline group were 26.2%, 12.9%, and 60.9%, respectively. The overall recovery rates were 40% for the steroid group and 39.1% for the pentoxifylline group (p=0.826). Table 4 summarizes the hearing recovery of the 2 groups after 3 months. Statistical differences of the hearing recovery rates were not significant between the 2 groups.

Table 5 demonstrates average FBS levels and occurrences of acute hyperglycemia between the treatment groups. The mean FBS levels were 203.9±92.0 mg/dL in the steroid group and 174.4±54.8 mg/dL in the pentoxifylline group (p=0.033). Almost half (48%) of all steroid-treated patients developed acute hyperglycemia, whereas this occurred in significantly fewer pentoxifylline-treated patients (33.1%; p=0.044). The average FBS values during hospitalization were higher in the steroid group despite strict adherence to insulin therapy. Acute hyperglycemia episodes were also more common in the steroid group.

DISCUSSION

Systemic steroids are the standard recommended treatment and are widely used for treating ISSNHL [3]. However, steroids have been associated with uncontrolled hyperglycemia, which limits their use in patients with DM [17]. Intratympanic injection of steroids is considered to be a suitable alternative to systemic steroids as an initial treatment for diabetic ISSNHL patients. IT steroid treatment proved to be as effective as systemic steroid therapy in a cohort of Korean patients with ISSNHL and DM [7]. They received oral prednisolone for 10 days (n=48), IV prednisolone for 7 days followed by oral prednisolone for another several days (IV group; n=32), or injections of dexamethasone into the middle ear cavity within a 2-week treatment period (IT group; n=34). No significant between-group differences were observed in hearing gain and recovery rates. At the end of treatment, the mean hearing improvements were 20 dB in the IV group, 26.2 dB in the oral treatment group, and 25.8 dB in the IT group. Recovery rates, defined as hearing recovery ≥15 dB, were 66.7% in the IV group, 72.3% in the oral treatment group, and 79.4% in the IT group. However, 1 patient in the oral group and 2 in the IV group dropped out of the study because of uncontrolled hyperglycemia. In another study, Fukui et al. [18] examined clinical and audiologic characteristics of 148 ISSNHL patients, 25 (16.2%) of whom had type 2 DM. Twelve out of 17 diabetic patients who were treated with steroids needed more frequent use of insulin therapy during the treatment period for adequate blood sugar control. A retrospective study (n=67) reported that diabetic patients with SSNHL have better improvement in low-to-middle-tone hearing loss than high-tone hearing loss [19]. Interestingly, the study results demonstrated treatment benefits with high-dose steroid therapy, and the authors concluded that the use of high-dose steroid therapy in diabetic patients with ISSNHL is recommended despite the high risk of exacerbation of blood sugar levels.

To the best of our knowledge, the efficacy of pentoxifylline treatment has not previously been assessed in diabetic patients with ISSNHL. Our retrospective comparison of pentoxifylline with corticosteroids in the treatment of diabetic patients with ISSNHL found that pentoxifylline was not inferior to corticosteroid therapy.

DM may induce thrombotic and embolic events and increase blood viscosity and is therefore a possible risk factor of SSNHL. In view of the increasing prevalence of DM worldwide, treatment of ISSNHL in diabetic patients warrants therapy that does not exacerbate blood sugar levels and add to the global DM burden.

At baseline, demographics, auditory data, and DM variables did not significantly differ between the 2 groups (Table 2). According to the results listed in Tables 3 and 4, pentoxifylline used in our treatment protocol is apparently not inferior to a 2-week corticosteroid regimen. The overall recovery rates (including partial and complete recovery) were similar for the pentoxifylline and steroid groups (39.1% vs 40%; p=0.826). In a randomized controlled trial, where the AAO-HNSF definition was used for the recovery definitions, the overall recovery rate was 55%-59% after 14 days of corticosteroid therapy. [4] Our recovery rates were lower than those observed in the above study. However, the mean age of patients in that study was lesser than that in our study group (40-42 years vs 59-61 years). Moreover, all of our patients had DM, whereas the study mentioned above did not focus on diabetic patients.

As detailed in Table 5, there were significant between-group differences in the average FBS levels and occurrences of acute hyperglycemia. The average FBS levels were higher and acute hyperglycemia was more common in the steroid group. Chronic hyperglycemia has long been considered to be related to the generation of oxidative stress and is a risk factor for accelerated atherosclerosis. However, acute blood sugar fluctuations in diabetes have recently been documented as a contributing factor in oxidative stress, which may lead to cardiovascular events in patients with DM [20]. In our study, the average FBS levels could reflect chronic hyperglycemia and occurrences of acute hyperglycemia may reflect glucose fluctuations during the treatment period. Diabetic patients receiving steroid treatment may be at a higher risk of cardiovascular events than those receiving pentoxifylline therapy. In a study, diabetic patients with ISSNHL treated with steroids needed more frequent use of insulin for blood sugar control compared with

non-diabetic patients with ISSNHL [18]. Although no acute complication such as diabetic ketoacidosis or hyperosmolar hyperglycemic state was reported in our patients during steroid therapy, close attention to blood sugar control is still necessary.

This study has some limitations. First, the nature of retrospective analysis is a potential source for selection bias. Second, it is difficult to make comparisons among studies due to lack of a standard definition of hearing recovery. In the future, randomized trials that incorporate a standard definition of recovery are needed to compare the efficacy of pentoxifylline therapy with that of conventional steroid therapy. Studies providing long-term outcomes in the treatment of ISSNHL are also warranted.

CONCLUSION

Pentoxifylline therapy in our study resulted in similar hearing improvements compared with steroid therapy in diabetic patients with ISSNHL and was also associated with superior blood sugar control during hospitalization.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of the China Medical University Hospital.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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