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Abstract

BACKGROUND: Evidence suggests that glucocorticoids are important in the treatment of sudden hearing loss (SHL) and Meniere's disease (MD). However, different glucocorticoid administration methods may have a significant impact on treatment outcomes.

OBJECTIVE: This study aimed to investigate effects of different glucocorticoid administration methods on sudden hearing loss and Meniere's disease.

METHODS: In this study, glucocorticoids were administered orally in 18 patients, by retroauricular injection in 15 patients and by intratympanic injection in 15 patients. White blood cell (WBC) count, serum K^+, fasting plasma glucose (FPG), body temperature, heart rate and blood pressure were used to evaluate effects of glucocorticoids on patients with hearing loss. Visual analog scale(VAS) of pain and

sleep disorders were also surveyed, and pure tone audiometry (PTA) results were compared among groups to evaluate efficacy of different glucocorticoids administration methods.

RESULT: WBC count, heart rate and blood pressure were higher in patients taking oral glucocorticoids, while body temperature, serum K^+ and FPG levels did not change in all three groups. However, patients who received intratympanic injection of glucocorticoids experienced more pain, while those taking oral glucocorticoids reported more sleep impairment. Treatment efficacy on hearing loss was not significantly different among the three groups.

CONCLUSION: These findings suggest that systemic glucocorticoid administration can result in greater whole body responses than local administration, but with similar hearing treatment efficacy.

Keywords: Sudden hearing loss; Meniere's disease; Glucocorticoids; Administration method; Overall response

1. Introduction

Meniere's disease (MD) and sudden hearing loss (SHL) are common diseases leading to hearing impairment. Although their etiologies are poorly understood, they share similar pathological changes. Glucocorticoids are produced by the adrenal cortex and widely used to treat a variety of diseases. Glucocorticoids have been recognized to be effective in the treatment of hearing loss in otological diseases, especially in SHL, Meniere's disease and tinnitus (Chandrasekhar et al., 2019; Henk et al., 2019; Nevoux et al., 2018). According to the Guidelines for Diagnosis and Treatment of Sudden Deafness formulated in China in 2015, systemic administration of glucocorticoids is the first-line therapy for SHL, while intratympanic or retroauricular injection of glucocorticoids can be used as a remedial treatment. Similarly, the guidelines for the diagnosis and treatment of Meniere's disease published in China in 2017 also noted that oral or intravenous administration of glucocorticoids should be the first approach when vertigo or significant hearing loss occurs in Meniere's disease (Kong WJ, 2017). However, it is well documented that glucocorticoids have significant side effects, especially in patients with underlying diseases, including diabetes, hypertension, gastric ulcer, sleep disorders, and hepatitis B. Systemic glucocorticoids have more adverse effects, including immunosuppression, increased blood pressure, abnormal glucose and lipid metabolism, sodium retention, potassium ion efflux and osteoporosis. Although glucocorticoids are important in the treatment of ear disorders, their side effects cannot be neglected as they may aggravate the original symptoms or lead to target organ damage (van der Goes et al., 2014). Therefore, it is important to weigh the benefits and disadvantages of using glucocorticoids in at risk patients. Numerous studies have reported controversial results on the efficacy of local and systemic glucocorticoid treatments in SHL. Local administration has been reported to reduce the incidence of systemic adverse reactions

(Lavigne et al., 2016; Liebau et al., 2017). To date, only a few studies have compared the efficacy of different glucocorticoid administration methods in the treatment of various diseases. White blood cells (WBC) are an important part of the immune system that helps defend the body against an infectious pathogen. Blood pressure, blood glucose levels, and electrolyte balance are important in maintaining homeostasis. Heart rate and body temperature reflect cardiopulmonary functions and basic metabolism, respectively. Sleep quality not only has important biological significance but also affects patients' compliance with treatment. Therefore, in this study, body temperature, heart rate, blood pressure, WBC count, fasting plasma glucose (FPG), serum K^+, visual analog scale (VAS) of pain and sleep disturbances were used to evaluate overall patient response to glucocorticoids treatment via different administration routes.

2. Materials and Methods

2.1. Patients

Patients admitted to the Department of Otolaryngology, Third Affiliated Hospital of Sun Yat-sen University, for hearing loss or tinnitus between May 1, 2019, and August 30, 2019 were recruited. All patients enrolled had a confirmed diagnosis of SHL or Meniere's disease. All patients with MD met the criteria outlined in the Criteria for Diagnosis of MD approved by the Equilibrium Committee of American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) (Lopez-Escamez JA, et al) and had stage II or III disease. Patients with SHL met the criteria defined in the clinical practice guideline: sudden hearing loss（Stachler RJ, et al）. Exclusion criteria included: 1) patients with hearing loss associated with other diseases, such as auditory neuropathy, internal auditory canal tumors, otitis media, inner ear deformities and autoimmune inner ear diseases; 2) patients with severe systemic diseases, such as malignant tumors, severe hypertension, uncontrolled diabetes mellitus, cardiac diseases, chronic kidney diseases and hepatitis B with severely abnormal liver function; 3) patients allergic to any of the drugs used in the present study; and 4) patients who did not want to participate in the study or had mental disorders.

2.2. Study design

Hearing evaluation and retroauricular and intratympanic glucocorticoids injections were conducted by experienced otologists. Participants were divided into three groups based on the route of methylprednisolone administration: i.e. oral, retroauricular or intratympanic injection. Magnetic resonance imaging (MRI) of the internal auditory canal, computed tomography (CT) of the temporal bone, and magnetic resonance angiography (MRA) of the brain were performed to exclude other diseases such as acoustic neuroma, meningioma, inner ear malformation and stroke. Routine audiometry was performed to determine the type and extent of hearing loss. Simultaneously, in addition to methylprednisolone, patients also received drugs aimed to improve microcirculation, nourish nerves and dissolve blood clots. Patients in the oral glucocorticoids group took the medicine upon diagnosis of hearing loss. However, patients in the other two groups received retroauricular and intratympanic glucocorticoids injection after failing oral glucocorticoids therapy before admission but demonstrated strong intentions to continue with treatment. In these patients, the interval between oral and local glucocorticoids administrations was at least 3 days to ensure no overlap between oral and local glucocorticoid effects, given that *in vivo* biological half-life of methylprednisolone is less than 36 hours.

2.3. Glucocorticoids administration

Patients in the oral glucocorticoids group received daily Medrol (1 mg/kg, maximum dose= 48 mg), with dose tapering after one week. For retroauricular injection, 1 ml of methylprednisolone (40 mg/ml) was injected obliquely at upper 1/3 of the postauricular sulcus (over the suprameatal triangle of the temporal bone) into the periosteum behind the external auditory canal on the affected side. Catton balls compression was used to control any bleeding. For intratympanic injection, patients were positioned in a lateral supine position with the affected ear facing upward, and the tympanic membrane was anesthetized with topical tetracaine (1%). The external auditory canal was prepped with alcohol, and 1ml of methylprednisolone (40 mg/ml) was injected via the anterior and

inferior quadrant of the tympanic membrane. The patient was instructed to avoid swallowing and speaking, and lie in bed for 30 minutes. Retroauricular orintratympanic injection was repeated once every two days, for a total of four times.

2.4. Biomarkers and blood tests

Body temperature, heart rate and blood pressure were measured in a resting state and quiet room the next morning following admission. WBC count, blood electrolytes and FPG were determined using venous blood samples before treatment and repeated after treatment. Audiometric testing was performed before and after treatment to evaluate treatment efficacy, using a Dandelion Tingmei 1081 audiometer in a soundproof room that met international standards. The air conduction pure tone average (PTA) threshold over 0.5, 1, 2 and 4 kHz was recorded. VAS scores of pain were taken from patients in the retroauricular and intratympanic injection groups. Besides, all participants completed a sleep survey after treatment. Patients were considered to have sleep disorders if they complained of experiencing difficulty in falling asleep or early awakening.

2.5. Statistical analysis

All continuous variables, including age, WBC count, serum K^+, FPG, VAS score and PTA, were presented as mean ± SD (standard deviation). Categorical variables, such as gender and treatment efficiency were presented as in percentage. Mann-Whitney *U* test was used to assess the statistical significance of differences between groups when the data were not normally distributed. The student's *t*-test was used to analyze normally distributed data. One-way analysis of variance (ANOVA) followed by Turkey's post hoc analysis was used to analyze clinical parameters before and after treatment in all three groups. Hearing improvement in dB was analyzed by

the chi-square test across the groups. $P<0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS 22.0 software.

2.6. Ethics Statement

The Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University approved the present study following the guidelines in the Declaration of Helsinki of 1975. All study participants presented a written informed consent to the tests for the levels of WBC, serum K^+ and fasting plasma glucose (FPG).

3. Results

3.1. Patient characteristics

In this study, 18 patients (nine males, 50%) took oral glucocorticoids only, 15 patients (eight males, 53%) received retroauricular glucocorticoid injection, and 15 patients (seven males, 47%) received intratympanic glucocorticoid injection. The mean age was 39.56±13.40 years for patients in the oral glucocorticoid only group, 43.73±13.13 years for those in the retroauricular injection group and 39.93±9.03 years for those in the intratympanic injection group, respectively (P=0.571). The demographic characteristics and clinical data of all patients are presented in **Table 1**.

3.2. Body temperature, heart rate and blood pressure

In the present study, body temperature was not significantly different among patients in the three groups (**Table 2A**), but post-treatment heart rate of patients in the oral glucocorticoid only group (89.42±6.58/min) was higher when compared with patients in the retroauricular (80.80±11.52/min, P=0.017) and intratympanic (81.27 ± 9.38, P=0.025) glucocorticoid injection groups (**Table 2A**), with no significant

difference between the latter two groups. Furthermore, after treatment, patients taking oral glucocorticoids had significantly higher systolic blood pressure levels (132.56±11.49 mmHg), when compared with patients in the intratympanic glucocorticoid injection group (121.87±8.74 mmHg, *P*=0.035)(**Table 2A**), although there was no significant difference in diastolic blood pressure among the three groups.

3.3. WBC, FPG and serum K^+

In this study, a significant increase in WBC count was observed in patients taking oral glucocorticoids (12.89±1.96 $x10^9$/L), when compared with patients in the retroauricular (9.33±2.63 $x10^9$/L, *P*=0.001) and intratympanic glucocorticoid injection (10.15±3.26 $x10^9$/L, *P*=0.013) groups (**Table 2B**), with no significant difference between the latter two groups. No significant difference in FPG and serum K^+ levels was observed among the three groups (*P*=0.192 and *P*=0.254, respectively) (**Table 2B**).

3.4. Pain and sleep

VAS pain scores were not recorded in patients taking oral glucocorticoids only given that oral medicine does not cause pain. Interestingly, patients receiving intratympanic glucocorticoid injection reported higher VAS pain scores compared with those receiving retroauricular injection (4.87±1.55 *vs*. 1.53±0.64, *P*<0.0001) (**Table 2B**). Moreover, during the administration of medicine, more patients taking oral glucocorticoids (72.22%) suffered from sleeping disorders, compared with patients receiving retroauricular (40.00%) or intratympanic (26.67%) glucocorticoid injection (*P*=0.025, **Table 3**), with no significant difference between the latter two groups.

3.5. Hearing improvement

Statistical analysis showed no significant difference in therapeutic efficacy in

terms of hearing improvement among the three groups according to the guidelines for diagnosis and treatment of sudden deafness (2015) (*P*=0.946, **Table 4**).

4. Discussion

This study presented a number of interesting findings. Firstly, a pronounced increase in heart rate and blood pressure was observed in patients taking oral glucocorticoids, when compared with patients receiving local glucocorticoid injections. Secondly, blood tests revealed that, regardless of systematic or local glucocorticoid administration, WBC count was elevated, although especially so in patients taking oral glucocorticoids. Thirdly, VAS pain scores were lower in patients receiving retroauricular glucocorticoid injection than in patients receiving intratympanic injection, indicating less pain experienced by patients in the former group. Fourthly, oral glucocorticoids greatly impacted sleeping patterns. Finally, there was no significant differences in glucocorticoid treatment efficacy among all patients. To the best of our knowledge, this is the first study to investigate the impacts of different methylprednisolone administration routes on treatment responses in sudden hearing loss and Meniere’sdisease.

Glucocorticoids have been widely used in treating otological diseases (Metrailer et al., 2016; Stelmakh et al., 2018; Wright, 2015). Their therapeutic effects in treating SHL and MD were affirmed in the guidelines for the treatment of sudden deafness in 2015 and in guidelines for the diagnosis and treatment of Meniere's disease in 2017 in China. However, the pathogenesis of SHL and MD remains unclear, although pathogenesis of SHL is supported by the theory of vascular accidents and rupture of the inner ear window membrane (Grunert et al., 2017; Schreiber et al., 2010) and pathogenesis of Meniere's disease is mainly thought to involve endolymphatic

absorption disorders, inner ear ischemia, autoimmune disorders, among others (Sajjadi et al., 2008; Schuknecht, 1963). Glucocorticoids have significant anti-inflammatory effects (Astolfi et al., 2016; Lai et al., 2017; Maeda et al., 2005), which can help maintain internal environment stability and reduce membranous labyrinth hydrops by alleviating neuroedema, inhibiting release of inflammatory mediators around the lesion, repairing ion transporters and restoring function of the stria vascularis (Dai et al., 2011; Shi, 2011). However, systemic glucocorticoids application has limitations. First, systemic glucocorticoids can produce a variety of adverse reactions, including flushing, palpitation, elevated blood pressure, difficulty falling asleep, decreased immunity, weight gain and acne. Short-term systemic use of glucocorticoids can cause osteoporosis (Compston, 2018; Creber et al., 2019). Therefore, systemic use of glucocorticoids is a relative contraindication for patients with several underlying diseases, especially type-2 diabetes, hypertension and coronary heart disease. Second, due to the existence of the blood-inner ear barrier, drug concentration in the inner ear is often insufficient, requiring a larger dose of glucocorticoid therapy, which undoubtedly increases the possibility of systemic reactions (Creber et al., 2019; Parnes et al., 1999). The effects of glucocorticoids via retroauricular or intratympanic injection in SHL and MD have been confirmed in several studies (El Sabbagh et al., 2017; Gao et al., 2017; Viana et al., 2014). The glucocorticoids absorption pathway via retroauricular injection is not very clear. However, a number of animal experiments have hypothesized that retroauricularly injected glucocorticoids can return to the sigmoid sinus *via* the retroauricular vein, maintaining its high concentration for a long time in this area and subsequently absorbed by the inner ear lymph (Fooken Jensen et al., 2016; Mulazimoglu et al., 2017). Glucocorticoids directly injected in the intratympanic chamber can accumulate

next to the round window membrane with high local concentrations while most of unabsorbed drugs are discharged through the eustachian tube (Plontke et al., 2009). Both retroauricular and intratympanic injection of glucocorticoids can circumvent the blood-inner barrier, and allow direct exposure of inner ear tissue to glucocorticoids, as well as less systemic exposure and fewer side effects. Methylprednisolone can directly bind to receptors in the inner ear, which can not only increase local drug concentration, but also reduce systemic drug exposure. Compared with other glucocorticoids, methylprednisolone has a high local concentration, allowing intracellular activity maintained for a longer period for an enhanced role of neuroprotection (Parnes et al., 1999; Sekiya et al., 2001; Zhou et al., 2009). Therefore, methylprednisolone was chosen as the therapeutic drug in this study. PTA improvement was slightly better with oral glucocorticoids than with retroauricular or intratympanic injections, although with no statistically significant difference. In this study, systemic glucocorticoids elevated WBC count. Glucocorticoids can promote the production of neutrophils in the bone marrow and thus the number of neutrophils in the blood. However, leukocytes chemotaxis is weakened (Ince et al., 2018). Fay et al found that glucocorticoid administration influenced leukocyte demargination and led to an increase in white blood cell count (Fay et al., 2016). Our study suggests that systemic administration of glucocorticoids is associated with greater inhibition of immunity as compared with local administration. On the other hand, our results also suggest that it is important to distinguish between glucocorticoids-induced and infection induced peripheral blood leukocyte elevation. Further research is needed to investigate the extent to which leukocytes function is affected. When compared with local glucocorticoids administration, oral glucocorticoids were associated with higher blood pressures. Glucocorticoids-induced hypertension is well known in clinical

practice (Sato et al., 1995); although the precise mechanisms have not yet been elucidated. The cytoplasm of vascular smooth muscle cells contains steroid receptors. Glucocorticoids can bind to and activate these receptors and increase vasoconstrictor receptors on vascular smooth muscle cells, including adrenergic receptors, vasopressin receptors and angiotensin receptors. Glucocorticoids also regulate blood pressure by inhibiting the production of prostacyclin, nitric oxide and other vasodilator mediators by endothelial cells (Goodwin et al., 2012). The present study shows that glucocorticoids can cause hypertension, although mainly affecting systolic pressure, suggesting that priority should be given to local drugs administration, especially among the elderly and hypertensive patients and those with poor blood pressure control. Besides, blood pressure should be closely monitored in the patients on systematic glucocorticoids to prevent cardiovascular and cerebrovascular accidents. Heart rates in patients taking oral glucocorticoids were significantly higher than those taking local glucocorticoids in this study, similar to results reported in patients with pemphigus and multiple sclerosis (Pishgahi et al., 2018; Vasheghani-Farahani et al., 2011). The mechanism by which glucocorticoids increase heart rate may involve water and sodium retention. However, one previous study reported glucocorticoid-associated bradycardia in children (van der Gugten et al., 2008). One possible explanation is that treatment dose and patient age may influence drug effects. In this study, oral glucocorticoids showed greater effects on sleep than locally administered glucocorticoids, which is consistent with previous studies (Costello et al., 2017; Patel et al., 2018). This is important since sleep quality can affect a patient's decision towards treatment. Interestingly, after treatment, there was no significant increase in FPG in all patients in this study, contradicting previous studies (Li et al., 2017). A possible explanation may be that most patients in the present study had no

type-2 diabetes, or they received excellent diabetes management. There was no significant difference in body temperature and serum potassium level among all the patients, suggesting that short-term use of glucocorticoids has little effect on body temperature and serum potassium. Furthermore, there was no significant difference in WBC count, blood pressure, heart rate, body temperature or serum potassium between retroauricular and intratympanic glucocorticoid injection groups, supporting that local routes may be preferable in patients with underlying diseases. A comparison of VAS pain scores in patients receiving retroauricular and intratympanic injection showed better pain experience in the former group than the latter during treatment.

In conclusion, this study suggests that glucocorticoid treatment is effective in the treatment of SHL or MD. However, oral glucocorticoids have a greater overall treatment impact in patients with underlying diseases, such as hypertension, diabetes mellitus, and coronary heart disease. Retroauricular or intratympanic glucocorticoids injection may be a better choice for these patients.

There were several limitations in this study, which should be realized: 1) participant sample size was small; 2) observation time was short; 3) findings could have been influenced by diet and other activities; 4) physiological cyclic body temperature changes in female patients were not considered; and 5) different disease stages could potentially affect patient's response to treatment. These limitations may have resulted in bias. Therefore, large scale studies with longer observation times are needed in the future with more sophisticated methods to determine treatment efficacy.

5. Conclusion

Oral administration of methylprednisolone increases hypertension and heart rate. Both systemic and local administration of methylprednisolone can increase WBC count, more so when administered orally. Patients receiving oral methylprednisolone

are more likely to suffer from sleep disorders, while those receiving intratympanic injection may experience more pain. These results suggest that oral administration of methylprednisolone may have a greater impact on overall treatment response in patients with SHL or MD.

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Potential Conflicts of Interest The authors have declared that no competing interests exist.

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Table 1. Demographic and clinical data

	Oral	Retroauricular injection	Intratympanic injection
Male n (%)	9 (50)	8 (53)	7 (47)
Femal n (%)	9 (50)	7 (47)	8 (53)
Age (year±SD)	39.56 ± 13.40	43.73± 13.13	39.93 ± 9.03
Hypertension n (%)	3 (17)	2 (13)	2 (13)
Diabetes n (%)	2 (12)	2 (13)	2 (13)
Tinnitus n (%)	14 (77)	11 (73)	13 (86)
Vertigo n (%)	5 (27)	5 (38)	6 (40)

SD- standard deviation

Table 2A. Clinical parameters before and after treatment in Mean (SD)

	Body temperature		Heart rate		SBP		DBP	
	Before	After	Before	After	Before	After	Before	After
Oral	36.49(0.11)	36.58(0.12)	77.72(6.34)	89.42(6.58)	121.27（13.01）	132.56（11.49）	76.67（10.90）	83.17（8.45）
Retroauricular injection	36.53(0.16)	36.55(0.11)	76.47(7.59)	80.80(11.52)	123.20（15.64）	126.47（14.74）	76.93（8.70）	77.73（9.60）
Intratympanic injection	36.59(0.10)	36.51(0.74)	76.90(6.81)	81.27(9.38)	121.13（9.98）	121.87（8.74）	77.04（9.01）	79.69（8.41）
t value	2.063	1.964	0.206	5.338	0.211	3.36	0.044	2.639
P	0.139	0.152	0.815	0.008**	0.81	0.043*	0.957	0.082

**$p < 0.01$, *$p < 0.05$. Abréviations: SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 2B. Lab results before and after treatment and pain score during treatment in mean (SD)

	WBC		K^+		FPG		VAS
	Before	After	Before	After	Before	After	
Oral	6.25(0.66)	12.89(1.96)	3.81(0.27)	3.60(0.32)	5.14(0.74)	5.04(0.63)	
Retroauricular injection	7.08(0.88)	9.33(2.63)	3.92(0.43)	3.78(0.60)	5.58(0.77)	5.51(1.06)	1.53（0.64）
Intratympanic injection	6.59(1.63)	10.15(3.26)	3.71(0.25)	3.82(0.23)	5.02(0.48)	5.50(0.82)	4.87（1.55）
t value	1.895	8.424	1.514	1.411	2.289	1.712	-4.551
P	0.162	0.001**	0.231	0.254	0.07	0.192	0.000***

***$p < 0.001$, **$p < 0.01$

Table 3. Sleep disorders following treatment

	Sleep disorder	No sleep disorder	X^2	*P*
Oral group	13	5	7.352	0.025*
Retroauricular injection	6	9		
Intratympanic injection	4	11		

*$p < 0.05$. One-way analysis of variance (ANOVA)

Table 4. Hearing improvement after treatment

Treatment route		Hearing Improvement （dB±SD）	Hearing improvement category			
			No change	Some improvement	Significant improvement	Complete resolution
Oral	18	27.44±12.71	3	4	8	3
Retroauricular injection	15	29.13±10.66	2	3	9	1
Intratympanic injection	15	28.47±10.20	2	3	9	1
X^2		0.93				1.695
p		0.91				0.946

Chi-square test