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นิพนธ์ต้นฉบับ Original Article

Intratympanic Steroids for Treatment of Sudden Hearing Loss after Failure of Oral Steroids Therapy

การฉีดยาสเตียรอยด์ผ่านเยื่อแก้วหูเพื่อรักษาประสาทหูเสื่อมเฉียบพลันที่ใช้ยาสเตียรอยด์แบบรับประทานรักษาแล้วไม่ได้ผล

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ABSTRACT

Objective : To evaluation treatment with intratympanic steroid (dexamethasone) for sudden sensorineural hearing loss after failure of oral steroid (prednisolone) treatment.

Materials and Methods : Randomized prospective controlled clinic trail. 100 patients presenting with idiopathic sudden sensorineural hearing loss were treated with prednisolone orally (1 mg./kg/day) for seven days. After this period, patients with treatment failure (36 cases) were randomized offered intratympanic steroid injection. 18 patients received three weekly 0.5 ml. injections of dexamethasone (4 mg/ml.), whereas the other 18 patients were treated orally at least 14 days. Recovery was reported as improvement of hearing more than 15 dB in pure tone average or an increase in Speech Discrimination Score (SDS) of 15% or greater.

Results : Intratympanic steroid treatment adding improved hearing loss in ten patients (55%) compared to standard oral steroid treatment ($P<0.05$). No serious adverse effects were observed.

Conclusion : Intratympanic steroid are an effective and safe rescue therapy in sudden sensorineural hearing loss cases that are refractory to standard treatment and might be a preferable choice as initial therapy.

บทคัดย่อ

วัตถุประสงค์ : ประเมินประสิทธิภาพของการฉีดยาสเตียรอยด์ (เด็กซาเมตทาโซน) ผ่านเยื่อบุแก้วหูเพื่อรักษาประสาทหูเสื่อมเฉียบพลันหลังจากใช้ยาสเตียรอยด์แบบรับประทานแล้วไม่ได้ผล

วัสดุและวิธีการ : ศึกษาข้อมูลผู้ป่วยประสาทหูเสื่อมเฉียบพลัน 100 ราย ซึ่งได้รับการรักษามาตรฐานโดยใช้ยาสเตียรอยด์แบบรับประทาน (เพร็ดนิโซโลน 1 มก./กก./วัน) เป็นเวลา 7 วัน นำกลุ่มที่ไม่ตอบสนองการรักษา 36 ราย นำมาแบ่งแบบสุ่มเลือกผู้ป่วยเป็น 2 กลุ่ม โดยกลุ่มแรก 18 รายให้การรักษาโดยการฉีดยาสเตียรอยด์ผ่านเยื่อบุแก้วหูโดยฉีดเด็กซาเมตทาโซน 0.5 ลบ.ซม. (4 มก./ลบ.ซม.) 1 ครั้งต่อสัปดาห์เป็นเวลา 3 สัปดาห์ และอีก 18 รายเป็นกลุ่มควบคุมให้การรักษาโดยการให้ยาแบบรับประทานต่อไปอย่างน้อยจนครบ 14 วัน ประเมินผลโดยการวัดค่าเฉลี่ยการได้ยินเปรียบเทียบก่อนและหลังการรักษาครบ, ถือว่าการรักษาได้ผลหากการได้ยินเฉลี่ยดีขึ้นมากกว่า 15 เดซิเบล

ผลการทดลอง : การฉีดยาสเตียรอยด์ผ่านเยื่อบุแก้วหูทำให้ผู้ป่วยมีอาการดีขึ้น 10 ราย (55%) เพิ่มเติมจากการรักษามาตรฐาน ($p < .05$), ไม่พบผลข้างเคียงที่รุนแรง

สรุป : การฉีดยาสเตียรอยด์ผ่านเยื่อบุแก้วหูมีประสิทธิภาพในการรักษาประสาทหูเสื่อมเฉียบพลันหลังจากใช้ยาสเตียรอยด์แบบรับประทานไม่ได้ผลและอาจพัฒนาเป็นการรักษาเบื้องต้นได้ในอนาคต

Introduction

Sudden Sensorineural hearing loss (SSNHL) usually presents as an acute unilateral deafness, with an abrupt onset, generally within three days, of more than 30dB hearing loss at three consecutive frequencies. The etiology of SSNHL remains idiopathic but viral infection, vascular compromise and immunologic diseases are the most discussed causes. The treatment of SSNHL remains controversial. Different approaches have been suggested : steroids, vasodilator, antiviral agents, diuretics and low-salt diets. Nevertheless, spontaneous recovery rate without treatment ranges from 30% to 60%, most resolving within 2 weeks after onset.[1]

As a result of its anti-inflammatory effect, high-dosage steroid therapy (oral or intravenous) is currently the mainstay of the treatment for SSNHL. Despite oral or intravenous steroid therapy for 2 weeks, approximately 30% to 50% of patients show no response.[1,2] Based on animal studies, intratympanic steroid injections have been proposed as treatment for SSNHL.[2,3] Introducing steroids through the tympanic membrane results in reduced systemic steroid toxicity and higher perilymph steroid level selectively.[1-4] Their use as secondary-line therapy in SSNHL refractory cases has been reported by several authors.[5-17] Its promising results have made some authors promote its use as first-line therapy in all SSNHL cases.[1,2,18,19]

Nevertheless, few controlled studies have been published comparing the results between intratympanic steroid treatment and other approaches.[6,19,20] The purpose of this study is to evaluate the effect of intratympanic steroid injections in patients with SSNHL after failure to standard oral steroid treatment.

Materials and Methods

From January 2001 to October 2008, data for trial was conducted from 100 patients presenting with idiopathic SSNHL. Informed consent was obtained from all patients. The present study was approved by the ethical review boards of Samutsakorn Province, intratympanic placebo injection did not allowed to

do as controlled.

100 consecutive patients presenting with unilateral SSNHL were entered into the study. All patients underwent a complete clinical history, physical and audiologic examination, syphilis serology, autoimmune antibody test and magnetic resonance imaging, which were negative.

Patients were excluded if SSNHL might be caused by trauma, Meniere's diseases, tumors and autoimmune diseases or diagnosed after that. Also, patients who were treated later than 30 days after onset of SSNHL were also excluded.

All Patients were treated with 1 mg/kg/day of oral prednisolone over seven days. Rest, cessation of smoking were also advised. Antiviral agents, diuretics other herbal or traditional medication were not included in our standard protocol. After seven days of prednisolone treatment, pure-tone audiometry and speech discrimination test (SDT) were performed. Pure-tone average (PTA) was calculated as the average of the thresholds at 0.5, 1, 2 and 3 kHz, following guidelines from Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery for evaluation and reporting hearing loss.

After this period of oral therapy, patients with treatment failure (36 cases), randomized 18 patients were received three weekly intratympanic injections of dexamethasone, other considered as controls were treated with oral steroid tapering over 14 days. Ethical board didnot allowed intratympanic injections of placebo.

Intratympanic steroid treatment was started after conservative treatment failed. The procedure was performed at supine position under a microscope. After confirmation of an intact tympanic membrane, local anesthesia was achieved with topical phenol (88% phenol, prepared at our Pharmacy Unit). Using a 24-gauge needle and 1-ml syringe, a posteroinferior puncture was made for perfusion. Dexamethasone (4 mg/ml) was instilled through this site in the dose of 0.5 ml approximately. The patient was instructed to avoid swallowing of moving in the supine position with the head tilted 45 degrees to the healthy side for 15 minutes.

Pure-tone audiometry and SDT were performed just before each injection and one week, one month and six months after the last injection. In the control group who refused intratympanic treatment, pure-tone audiometry and SDT were performed one month and six months after onset.

Recovery of hearing was defined as improvement of more than 15 dB in PTA or an increase in Speech Discrimination Score (SDS) of 15% or greater. Threshold differences were also analyzed at each frequency in PTA. Side effects and subjective symptoms were also recorded.

Statistical analysis was done with use of SPSS 15.0, at 0.05 significance, indicating standard deviations (SDs) when needed. Qualitative variables were compared with x^2 and McNemar tests, whereas quantitative variables were done with Student's *t* and Wilcoxon nonparametric tests. Multivariate analysis was also performed.

Results

140 patients presented to our hospital with idiopathic SSNHL during the study period. Never-

Table 1 Idiopathic sudden sensorineural hearing loss data

Number	100	
Sex	Male 44	
	Female 56	*(P < 0.05)*
Time onset	7.5 day	(± 7.1 SD)
Initial hearing level	78.5 dB.PTAs	(± 20.2 SD)
	36% SDS	(± 14 SD)
Mean Hearing improvement by oral steroid (N = 64)	36.0 dB PTAs	(± 16.54 SD)
		(P = .001)

Table 2 Failure oral prednisolone group

	Controlled	**IT-Dexa**	**P**
N	18	18	*Non sig*
Mean PTAs before (dB)	74.5 (± 26.7 SD)	73.3 (± 20.8 SD)	*Non sig*
Mean PTAs after (dB)	72.3 (± 24.7 SD)	40.2 (± 17.3 SD)	*P = .001*
PTAs Improvement (dB)	2.2 (*P* > .005)	33.1 (*P* < .001)	*P* = .001

* no statistical differences in age, sex ratio, time of onset to therapy, presence of vertigo and tinnitus, initial hearing level and final hearing level after oral treatment between the two groups.

Table 3 Outcome, compare between oral treatment compared to intratympanic treatment

	Oral prednisolone	**IT-dexamethasone**	**Controlled of IT-dexamethasone**
Improvement 15 dB	64 (N = 100)	10 (N = 18)*	0 (N = 18)
Mean PTA improvement	36.0 (± 16.54 SD) (*P* = .001)	33 dB (± 12.50 SD) (*P* < 0.001)	2.2 Db (*P* > .005)

theless, 40 patients were excluded from criteria. Therefore, 100 patients were enrolled in the study. The average age of the patients was 52.0 years (± 15.8 SD). The male-to-female ratio was 44 : 56. Time of onset of oral therapy averaged 7.5 days (± 7.1 SD). Initial hearing impairment was an average of 78.5 dB PTA (± 20.2 SD) and 36% SDS (± 14 SD). Tinnitus was present in 48% of the patients, whereas vertigo was present in 32%. Thirty patients had hypertension and 16 patients had diabetes mellitus.

After standard oral treatment, hearing improvement of 15 dB or more in PTA was noted in 64 patients (64%). In these responders, the mean improvement of the value of PTAs before and after oral treatment was 36.0 dB (± 16.54 SD), showing statistical significance (P = 0.001). There were no statistical differences in hearing improvement compared with age (P = 0.162), sex ratio (P = 0.317), and presence of vertigo (P = 0.918) or tinnitus (P = 0.127). Initial PTA (P = 0.001) and time of onset to therapy (P = 0.004) showed a significant relation with the grade of hearing recovery. Multivariate analysis by multiple regression confirmed that onset to therapy after seven days was related to lesser hearing improvement ; 12 dB versus 26 dB on average.

Patients with treatment failure (36 cases) were then included in intratympanic treatment study. Eighteen patients were enrolled in the treatment group, whereas the other eighteen served as internal controls. There were no statistical differences in age, sex ratio, time of onset to therapy, presence of vertigo and tinnitus, initial hearing level and final hearing level after oral treatment between the two groups.

In the treatment group, hearing improvement of 15 dB or more in PTA was noted in ten patients (55%). The mean values of PTAs before and one month after intratympanic injection treatment were 73.3 dB (± 20.8 SD) and 40.2 dB (± 17.3 SD), respectively, so that an improvement in mean PTA after intratympanic treatment was 33 dB (± 12.50 SD), showing statistical significance (P = 0.001). In the control group, the mean values of PTA after oral treatment and one month after onset were 74.5 dB (± 26.7 SD) and 72.3 dB (± 24.7 SD), respectively ; this difference was not statistically significant. Conclusively, there was much more hearing gain in the treatment group (33.1 dB) than in the control group (2.2 dB), showing, again, statistical significance (P= 0.001)

In the intratympanic treatment group, hearing improvement occurred after the first injection in two patient, after second injection in four patients whereas the other four responders improved after the third injection. Multiple regression analysis show onset to therapy after 7 days was related to less hearing improvement. No relevant secondary effects were seen after intratympanic injections. Only four patients showed temporary dizziness, which seemed to be caused by caloric effect of instillation of the drug. Burning sensation and pain were minimal when dexamethasone was instilled.

In summary, from an initial population of 100 patients, intravenous treatment achieved hearing recovery in 64 patients (64%) whereas intratympanic injections allowed restoration of useful hearing in an additional ten patients (55% of treated cases).

Discussion

High-dosage systemic steroid therapy has become widely used for treatment of SSNHL. However, a few patients may experience adverse effects during systemic steroid therapy such as gastrointestianl problems, gluteal abscess formation, and avascular necrosis. These side effects are more common among patients with hypertension or diabetic mellitus, which are common disorders in SSNHL patients.[1,4,20]

Furthermore, after oral or intravenous high-dosage steroid therapy, approximately 30% to 50% of patients show no response.[1,2,6] In these refractory patients, based on amimal studies, intratympanic steroid injections have been proposed as rescue therapy.[2,3] It allows an increase in local concentration of sterorids at the inner ear through the tympanic membrane and results in reduced systemic steroid toxicity.[1,4] Parnes, et at,[2] also reported that methylprednisolone showed more effective absorption than dexamethasone.

Various reports on the effect of intratympanic steroid injection in idiopathic SSNH have been published.[2-20] Although these previous studies have some limitations, such as a small number of subjects and the lack of control groups, the effect of intratympanic steroid injection on hearing recovery is similar to that of systemic steroid therapy. Nevertheless, their success are very variable between series. This may be related to different intratympanic regimens and doses but also to the time to onset of treatment after failure of conventional medication and to the way in which satisfactory results have been reported. For instance, Guan-Min, et al,[6] used a scale that accepted successful treatment (53%) when PTA improvement was greater than 30 dB, whereas Battista accepted only a partial success (12%) when hearing was improved to a final PTA with greater than 50% of hearing.[9] Reporting the mean PTA improvement after treatment might be a more objective outcome measure, as is reported in this paper

A delay of longer than 10 days before the start of intratympanic treatment has been reported to lead to a significantly worse hearing outcome.[18] This is also confirmed in our study by multiple regression analysis : onset to therapy after 7 days was related to less hearing improvement. This fact might also explain those series with less effective results after intratympanic treatment.[9,16] For instance, Battista[9] has reported only partial success in 12% of patients, but the mean and median delays to start therapy were 28 and 18 days, respectively(range, 2 to 180 days).

As shown in this study and the literature. Intratympanic steroid injection is very useful as a secondary treatment after the initial systemic treatment of idiopathic SSNHL.[1-5] Nevertheless, it is not totaly clear whether this effect is actually from intratympanic steroid, natural pathophysiological coures or delayed effect of systemic steroid previous treatment.[4]

Few controlled studies have been published comparing the results between intratympanic steroid treatment and other approaches as salvage treatment in SSNHL.[6,10,17,19,20] Guan-Min, et al,[6] reported a prospective randomized trial after failure with oral steroid treatment over 10 days. Fifty-three percent showed hearing improvement (mean PTA improve-

ment was 28 dB) after intratympanic dexamethasone treatment, compard with 7% of patients in the standard group (mean PTA improvement was 13 dB), a significant difference. Choung, et al,[10] presented a case- control study on SSNHL after failure with oral steroid treatment, comparing a prospective series on 33 patients who were treated by intratympanic dexamethasone with a retrospective group of 33 patients who had not been so treated. Hearing improvement was obseved in 39% of patients after intratympanic treatment (mean PTA improvement was 9 dB), whereas only 6% showed improvement when it was not used (mean PTA improvement was 2 dB), although this difference in mean PTA improvement was not significant.

Roebuck and Chang[17] published a prospective nonrandomized trial on SSNHL. After failure with oral steroid treatment, patients were advised on treatment options and self-selected into a group of 31 patients who were treated by intratympanic dexamethasone and a control group of 30 patients who were only treated with oral steroids. Hearing improvement was more frequent after intratympanic treatment (30% of patients and mean PTA improvement of 12 dB, versus 10% and 10 dB), although this difference in mean PTA improvement was not significant. Our prospective study was designed in a similar way but using patients who treated with oral steroids therapy as controls and showing similar but statistically significant, results (55% and mean PTA improvement of 33 dB, versus 0% and 2 dB). These findings have also been confirmed by Xenellis, et al.[19] These findings have also been confirmed by Xenellis, et al.[19] They have reported a prospective, randomized trial after failure with intravenous steroid treatment over 10 days. Nineteen patients received intratympanic methylprednisolone and 47% showed hearing improvement (mean PTA improvement was 15 dB), whereas a control group of 18 received placebo and did not show any improvement (mean PTA improvement was 0.8 dB), a significant difference.[19] In these series and ours, natural history or residual systemic steroid effect gave the control group a minimum hearing recovery. Therefore, hearing improvement seems to be related to intratympanic treatment in those patients who received it.

However, those results and ours are based on small sample sizes and variance in intratympanic treatment response is wide, between 12% and 100%. These facts limit the statistical evidence of our results-if, for example, the estimate variance is somewhere in the middle (50%) and the desired clinically significant difference between groups is around 20%, power and sample size calculation demonstrate the need for humdreds of subjects in each cohort (intratympanic versus no intratympanic) to confirm a statistically significant benefit of intratympanic therapy. Therefore, we need larger sample sizes to establish valid conclusions in the future.

Nevertheless, these promising results after failure of systemic steroids have made some authors promote its use as first-line therapy in all SSNHL cases.[18,20] Banarjee and Parnes[18] have reported successful hearing improvement in 50% (mean PTA improvement was 27 dB) when intratympanic methylpredmisolone was used as initial treatment. More recently, Kakaehata, et al,[20] published a case-control study, showing that intratympanic treatment is also

effective as initial therapy in SSNHL, with less toxicity than systemic steroids. They compared a group of 10 diabetic patients who were treated with intratympanic dexamethasone and showed successful hearing improvement in 70% (mean PTA improvement was 41 dB) compared with a historical group of 21 patients who were treated with intravenous dexamethasone and had successful hearing improvement in 67% (mean PTA improvement was 25 dB), a significant difference.[20]

After these good results, it seems that intratympanic treatment of SSNHL might be a preferable choice as initial therapy, as it has been shown as rescue after treatment failure. Future controlled studies with larger sample sizes will allow confirmation of these findings. These studies should include cohorts with hundreds of subjects to confirm a statistically significant benefit of intratympanic therapy of SSNHL.

Conclusion

This randomized prospective clinical trial shows that intratympanic dexamethasone significantly improves the outcome of SSNHL after intravenous steroid treatment. As reported in other control studies in the literature, intratympanic steroids actually are an effective and safe therapy in SSNHL case that are refractory to standard treatment.

Nevertheless, the number of injections, the type of steroid and the most adequate doses are still questionable and need more information.

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