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RESEARCH PAPER

Assessment of complications due to intratympanic injections

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Abstract *Objective:* The purpose of the study is to report and to analyze the complications following intratympanic injections (ITI) of steroids. The occurrence rate of complications at different ITI sites, four quadrants of eardrum, was also compared.
Methods: A retrospective clinical review in a medical center. Each patient received ITI twice in a week for 2–3 consecutive weeks as a salvage therapy for sudden sensorineural hearing loss. Post-injection complications, especially transient dizziness and vertigo, were recorded. Patients with acute or chronic vertigo episodes in 1 month were excluded.
Results: A total of 59 patients with sudden sensorineural hearing loss and a total of 278 times of ITI were performed in 1 year. The post-injection complications included pain, tongue numbness, transient dizziness, vertigo, tinnitus, and a small persistent perforation. There was no significant difference in the occurrence of these complications between the injections sites on the 4 quadrants of the tympanic membrane. However, there was statistical significance in the post-injection vertiginous episode after IT injections to posterior-inferior quadrant (Q3) and posterior-superior quadrant (Q4) compared to anterior-superior quadrant (Q1) and anterior-inferior quadrant (Q2) ($P = 0.0113$).

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Conclusion: IT injection is recommended to be applied to the Q2 since the Q1 and Q4 injections are more likely to induce the adverse effect of tongue numbness, while the Q3 and Q4 areas are more likely to induce post-injection vertigo.

Introduction

Corticosteroids are widely used for the treatment of Ménière's disease, sudden sensorineural hearing loss (SSNHL), autoimmune inner ear disease, and tinnitus. Oral treatment with steroid was reported to have 88% adverse effects, such as increasing requirements for insulin or oral hypoglycemic agent (OHA) in patients with diabetes mellitus (DM), increased thirst, and sleep or appetite changes. The intratympanic injection (ITI) was first used by Itoh to treat patients with Ménière's disease in 1991.[1] Silverstein was the first to use intratympanic steroids for the treatment of SSHNL in 1996. This method decreases the side effect of systemic steroid administration and leads to higher concentrations of the injected drug in the inner ear. Recently, many studies have shown the efficacy of corticosteroid use on the cochlear function in both human and animal models.[2] Despite wide-ranging investigations, only minimal information focused on the adverse effects induced by ITI of steroid. The complications of ITI include transient dizziness, injection pain, a burning sensation, increasing tinnitus, post-injection vertigo, tongue numbness, and a small perforation of the eardrum.[3] The most common side effect is transient dizziness, injection site pain, and a burning sensation. The character of post-injection vertigo has not been described in detail. This article will focus on the adverse effects of ITI and a characteristic description of post-injection vertigo. In order to prevent possible annoying side effects,[4,5] previous articles suggested injection of the solution into the posterior-inferior quadrant, via narrow-gauge spinal needle, to fill the middle ear space.[4] However, there is still no consensus to it.

Materials and methods

Patient selection

This retrospective clinical study was performed from January 1st, 2013 to December 25th, 2013 in a medical center. It included 59 patients with idiopathic sudden sensorineural hearing loss (ISSHL). Six out of 59 patients had severe vertigo attack along with sudden hearing loss for the initial 2 days, then vertigo subsided and followed by mild to moderate disequilibrium. All intratympanic steroid injected were used as a salvage treatment when primary treatment with oral steroid failed to improve hearing loss and tinnitus completely. The exclusion criteria are patients under active treatment for recurrent vertigo before ITI.

Intratympanic injection technique

The ITI procedure has been approved by ethic committee of this hospital as a standard procedure to treat sudden deafness. Before the procedure, an informed consent with a clear explanation of the different injection sites, the risks and benefits, and the local anesthesia (although there was evidence that the local anesthesia before ITI is not always necessary[3]), was obtained. Since there are no standard protocol of ITI in this hospital regarding how many injections should be administered to one treatment course, the injection times was determined by the two senior authors. One of them injected 4 times in a 2-week period and the other 6 times in a 3-week period. In total, 38 patients were injected 4 times and 21 were injected for 6 times, which made the total injection times of 278.

Each patient received ITI twice in a week, separated by at least 2 days, for 2 or 3 consecutive weeks. Because this is a retrospective review, the injection sites and criteria were not pre-designed. For both senior authors who did the injection, the sites were mainly dependent on the condition of the eardrum. Most often, the anterior inferior Q will be selected, other alterative sites was chosen under special conditions such as an unhealed perforation by prior injection or blot clot covering the preferred injection sites. We defined Q1 as the anterior-superior quadrant, Q2 as the anterior-inferior quadrant, Q3 as the posterior-inferior quadrant, and Q4 as the posterior-superior quadrant. Injections were administered in the out-patient clinic by the senior authors under operating microscope. Extreme care was taken to slowly inject the steroid into middle ear to avoid injury to the underlying structures despite of different injection sites. We used 20% lidocaine spray as the local anesthetic agent, which is applied and fills the external auditory canal 5 min before injections. In order to prevent a caloric reaction, we asked patients to warm up the injection agent by holding the syringe with drugs in their palm for 5—10 min to warm it to body temperature. The patient was asked to lie in a supine position, with the head turned 45° toward the unaffected ear. Medication was injected through 1 of the 4 different quadrants of the tympanic membrane with a Becton—Dickinson (BD) spinal needle (27 G, 3.50 in., 0.64 mm × 90 mm). Once the IT injection was administered, the patient was asked to keep the same position for 30 min to provide maximal absorption of the medication through the round window. Patients were asked not to speak or swallow to prevent drug leakage through the Eustachian tube. After each injection, patients were asked to report if they perceived intolerable pain, vertigo, or any discomfort immediately. In addition, at the next office hour, patients were requested to describe and

record any discomfort they suffered after leaving the clinic. We also checked the pure-tone audiometry before the course of IT injection, weekly during the course and 1 week after completion of the treatment course. Outcome improvement is defined as the difference of 5 frequencies (256 Hz, 512 Hz, 1024 Hz, 2048 Hz, and 4096 Hz). Average hearing level improved more than 10 dB after ITI.

Injection agent

The medication we chose was Rinderon Injection (Betamethasone Disodium Phosphate 5.3 mg/mL, as Betamethasone 4 mg/mL). The dosage was about 0.4—0.8 mL into the middle ear space for each injection, according to Clinical Practice Guideline.[4]

Measures and statistical analysis

The crew asked patients to report (immediately and 30 min after ITI) if there were any discomforts after ITI, such as vertigo, intolerable pain, tinnitus, ear fullness, burning sensation, or tongue numbness. This was repeated in the next office hour. We were also wary of eardrum perforations. We calculated the percentage of complications and also analyzed the relationship between injection sites at the tympanic membrane and complications, using Chi-squared test by SPSS 2.0.

Results

Complications after ITI

There were 59 patients (26 male, 33 female, average age 57.2 years old, left ear 29 cases, right ear 30 cases) who received ITI (278 times in total). The most common injection site was the anterior-inferior quadrant (Q2), 120 times (43.2%), followed by the posterior-inferior quadrant (Q3), the anterior-superior quadrant (Q1), and the posterior-superior quadrant (Q4). The injection times and percentages are 92 (33.1%), 35 (12.6%), and 31 (11.2%) respectively. The injection site depends on the different technique of the senior authors and the prior injection conditions such as clot or perforation. ITI was used as initial therapy for 17 (28.8%) patients. Steroid ITI was used as salvage therapy for 42 (71.2%) patients. Twenty-five (42.3%) cases had hearing improvement after ITI.

Increasing tinnitus was noted 15 out of 278 times (about 5.4%) after ITI. The transient dizziness and post-injection vertigo were noted 47 times (16.9%) and 5 times (1.8%), respectively, after injection. Most patients who received ITI underwent only mildly painful sensations, about 211 times (75.9%). There was one female who suffered from severe pain after ITI and refused further ITI therapy. The patients with underlying diseases, such as diabetes mellitus (DM), peripheral neuropathy, or a history of nasopharyngeal cancer status post-irradiation therapy or chronic otitis media with eardrum thickening, reported less pain during injection. The symptom of tongue numbness was reported by 2 patients, about 0.7%. The injection sites were the Q1 and Q4, respectively. One case had a small eardrum perforation after 6 times of ITI. A previous article reported that persistent tympanic membrane perforations are rare and most of them lasting up to 6 months.[4] The perforation site was on the Q2 area, and the wound healed spontaneously after 4 weeks of out-patient department (OPD) follow-up. The hearing recovery rate in our article is about 42.3%. The recovery rate is higher than that in a previous article (27.5%).[5]

Post-ITI vertigo cases

The acute onset transient dizziness episodes are quite frequent. They ranged from disequilibrium for several seconds to lightheadedness for a few minutes. The duration rarely lasted longer than 10 min. It does not affect the patient's ability to walk or his behavior. It was relieved spontaneously after a few minutes of rest.

Five patients had post-injection vertigo. They did not suffer from vertigo attack until 20—30 min after ITI, especially when getting up. We realized that the duration of post-injection vertigo ranged from 40 min to 5 h, and it was accompanied by persistent horizontal nystagmus to the unaffected ear. The visual suppression was positive in all five patients. Two patients had rotatory nystagmus to the left, and one patient had rotatory nystagmus to the right. The detailed data of these 5 patients are listed in Table 1. Two out of five patients recovered after ITI. Case 1 without previous medical history has a hearing improvement from an average hearing level of 85 dB—50 dB. Case 2 has a history of breast cancer, status post operation 2 years ago, now under hormone therapy. She also has hearing improvement from an average hearing level of 79 dB—7 dB. The other 3 cases did not have obvious hearing improvements.

Injection site and post ITI dizziness and vertigo

As shown in Table 2, the Q1 statistical accumulation showed 8 patients out of 35 patients, 22.9%, who experienced transient dizziness after ITI. The Q2 statistical accumulation showed 20 patients out of 120 patients, 16.7%, who experienced transient dizziness after ITI. The Q3 statistical accumulation showed 13 patients out of 92 patients, 14.1%, who experienced transient dizziness after ITI. The Q4 statistical accumulation showed 6 patients out of 31 patients, 19.4%, who experienced transient dizziness after ITI.

Although a difference in the percentage of transient dizziness rate is noted in each quadrant, it is not statistically significant and all P values >0.05.

Comparing the incidence of post-injection vertigo between the two protocols (4 times in 2 weeks vs.6 times in 3 weeks), the 4 times group is 1.58% and the 6 times group is 1.97%. This is based on injection numbers but not patient numbers. There is no statistical difference between these two protocols.

Discussion

The possible pathophysiology of post ITI vertigo is still unknown. The etiology may be due to the caloric test response, the lidocaine agent diffused into the inner ear,

Table 1 Five post-injection cases.

Number	Age	Sex	Oral steroid therapy	Lesion side ear	Quadrate	Rotation	Nystagmus direction	Duration	Vomiting	Hearing improvement
1	71	M	Yes	Right	Q3	No	Left	2 h 37 min	No	Yes
2	56	F	No	Right	Q3	Clockwise	Left	3 h	Yes	No
3	81	M	Yes	Left	Q4	Conterclock	Right	2 h 20 min	Yes	No
4	54	M	Yes	Right	Q3	Clockwise	Left	5 h	Yes	No
5	31	F	Yes	Left	Q4	No	Right	40 min	No	Yes

Q3, posterior-inferior quadrant, and Q4, posterior-superior quadrant; M, male; F, female.

Table 2 Injection sites and incidence of post-injection dizziness or vertigo.

Injection site (quadrant)	Transient dizzy rate	Post-injection vertigo rate
Q1	8/35 (22.9%)	0/35 (0%)
Q2	20/120 (16.7%)	0/120 (0%)
Q3	13/92 (14.1%)	3/92 (3.3%)
Q4	6/31 (19.4%)	2/31 (6.5%)

Q1, anterior-superior quadrant; Q2, anterior-inferior quadrant; Q3, posterior-inferior quadrant, and Q4, posterior-superior quadrant.

the semicircular canal dehiscence on the middle ear cavity side or the injection agent irritating the round window. The caloric response was first described by Robert Barany in 1906. It is a test of the lateral semicircular canals. Vertigo and nystagmus may be induced immediately by warm and cold media. The duration is usually within 10 min. The clinical course is different from what we observed in post-ITI vertigo, which has much longer vertiginous time with persistent nystagmus. Besides, we always ask patients to warm up the steroid agent in the palm for 5—10 min before injection. Therefore, the Caloric test response is less likely to be the major explanation of post-injection vertigo.

The lidocaine agent diffused into the inner ear is a possible explanation of post-injection vertigo, although we always try to clean the anesthetic agent completely before injection, we think that there is still possibility that the residual anesthetic agent may leak and diffuse into the inner ear. The semicircular canal dehiscence on the middle ear cavity side is rare and possible, but if such an anomaly pre-existed, the post-injection vertigo should happen every time after ITI. It seems it is also not likely to be the etiology of post-injection vertigo. Another possible etiology of the post-injection vertigo is the irritation of the round window by the injection agent, which makes a micro-perilymph fistula on it. But based on the anatomy and previous experience of cochlear implantation, round window is membrane is not so fragile and easily subjected to injury. Therefore, the micro-fistula is again less likely.

One limitation of the present study is its retrospective design, which may cause biased result. Also, the injection done a less favorable condition may be a confounding factor in analyzing the post injection complications. Finally, there is no plausible explanation for the post-injection prolonged vertigo in 5 patients. However, our results do suggest that injection on the posterior quadrant or under less favorable conditions may have higher incidence of vertigo. Therefore these sites should be avoided whenever possible.

Conclusion

The steroid IT injection performed is suggested to be applied to the anterior-inferior quadrant (Q2) since the Q1 and Q4 injections are more likely to induce the adverse effect of tongue numbness, though there was no statistical significance in our study. The injections to the Q3 and Q4 areas display statistical significance, compared to those of the Q1 and Q2 areas, with a greater possibility of causing post-injection vertigo.

Financial disclosure

No.

Conflicts of interest

Nil.

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