
Effectiveness of instillation of triamcinolone acetonide into the middle ear for eosinophilic otitis media associated with bronchial asthma

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Background: Eosinophilic otitis media (EOM) is a newly recognized middle ear disease found in asthmatic patients. EOM is characterized by a highly viscous middle ear effusion that contains many eosinophils and is extremely unresponsive to conventional treatments for common otitis media. To our knowledge, no systemic study regarding the efficacy of treatments for EOM has been performed.

Objective: To determine the effectiveness of instillation of triamcinolone acetonide, which is a suspension of steroids, into the mesotympanum and eustachian tube as a treatment for patients with EOM.

Methods: We studied the efficacy of the instillation of triamcinolone acetonide in 43 ears of 24 patients with EOM. Efficacy was evaluated according to the length of the period without middle ear effusion or otorrhea. We also determined the otomicroscopic findings and the hearing levels before and after therapy. For controls, 27 ears of 14 patients treated by topical administration of betamethasone were similarly evaluated.

Results: The middle ear effusion or otorrhea was controlled for more than 3 weeks after 1 instillation of triamcinolone acetonide in 35 ears, and the efficacy rate (81%) was significantly higher than that in the controls (7 ears, 26%). In the triamcinolone acetonide group, the average air conduction hearing level at the speech frequency range was significantly improved, and deterioration of the bone conduction hearing threshold was rarely found during therapy.

Conclusion: The instillation of triamcinolone acetonide into the mesotympanum and eustachian tube is an effective treatment for patients with EOM.

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INTRODUCTION

Eosinophilic otitis media (EOM) is a newly recognized middle ear disease observed in asthmatic patients. Patients with EOM exhibit clinical characteristics markedly different from those of common chronic otitis media or otitis media with effusion (OME). The middle ear effusion (MEE) is yellow and highly viscous, and patients experience hearing loss and otorrhea for a prolonged period and sometimes become either gradually or suddenly deaf.^{1–3} In 1997, Tomioka et al¹ named this condition EOM, because the MEE contains numerous eosinophils regardless of the presence of type 1 allergy.

Most patients with EOM are treated for OME or chronic otitis media for a long time, and the middle ear symptoms are extremely unresponsive to conventional treatments for the common types of otitis media, such as eustachian tube inflation, myringotomy or insertion of a tympanostomy tube for OME, and administration of antibiotics or ear surgery for chronic otitis media. Because general ear, nose, and throat (ENT) physicians have an increased awareness of EOM, several treatments have been tried to resolve the disease, such as topical administration of water-soluble steroids or heparin,⁴ oral or systemic adminis-

tration of steroids, pulse therapy using a steroid,⁵ and oral administration of anti- T_H2 cytokine inhibitors or leukotriene receptor antagonists. However, to our knowledge, no systematic study has been performed concerning the efficacy of these therapies for patients with EOM. We treated EOM patients using triamcinolone acetonide, a suspension of steroids, instilled into the middle ear and then forced to drain toward the eustachian tube by the application of positive pressure, because not only the middle ear but also the eustachian tube are the site of eosinophilic inflammation.⁶ Control of the pathologic changes in the eustachian tube seems to be the most important approach to resolving EOM. The present study was performed to determine the effectiveness of the instillation of triamcinolone acetonide into the mesotympanum and the eustachian tube for treating patients with EOM. We based effectiveness on the length of the period without MEE or otorrhea. In addition, we also determined the hearing levels before and after therapy, because patients with EOM frequently show progressive sensorineural hearing loss.

PATIENTS AND METHODS

Patients

Our study included 24 patients (18 women and 6 men; age range, 27–74 years) who were diagnosed as having EOM at the Department of Otolaryngology, Teikyo University Hospital, on the basis of the diagnostic criteria proposed by Nagamine et al² as follows: (1) precedence of and association with adult bron-

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Table 1. Baseline Patient Characteristics

Characteristics	Triamcinolone acetonide group	Control group
No. of patients (No. of ears)	24 (43)	14 (27)
F:M, No.	18:6	11:3
Age at the entry, mean $\pm$ SD (range), y	58 $\pm$ 11 (27–74)	46 $\pm$ 11 (28–57)
Atopic:nonatopic patients, No.	13:11	5:9
Aspirin intolerance, No.	7	6
Association of sinusitis (nasal polyposis), No.	21 (19)	12 (11)
Use of systemic steroids for bronchial asthma, No.	6	5
Duration of treatment, mean $\pm$ SD (range), mo	27 $\pm$ 19 (6–65)	40 $\pm$ 24 (11–72)

chial asthma (atopic or nonatopic) and (2) presence of yellow and extremely viscous MEE that predominantly contained eosinophils. The patients were treated with topical administration of triamcinolone acetonide and followed up for more than 6 months. Cytologic and histologic examinations of the MEE or middle ear mucosa revealed predominant infiltration of eosinophils in the specimens of all patients. Paranasal diseases were detected in 21 patients by nasal symptoms, rhinoscopic findings, and paranasal computed tomograms. Nasal polyposis was detected in 19 patients. Of the 24 patients, both ears were affected in 20 patients, and 1 ear had already been operated on. The remaining 4 patients showed unilateral otitis media. Therefore, a total of 43 ears were subjected to the present study. For controls, 27 ears of 14 patients diagnosed as having EOM using the same criteria and treated with the application of eardrops that contained betamethasone were also studied. The baseline characteristics of the patients in the 2 groups (topical administration of triamcinolone acetonide group and the control group) are given in Table 1.

Previous Otologic Treatments

The patients in both groups had been treated for OME or chronic otitis media at ENT clinics before visiting our hospital. Most of the patients underwent catheter inflation therapy (a metal inflation tube is placed in the nasopharyngeal orifice of the eustachian tube through the common nasal meatus and the air is insufflated into the eustachian tube via the metal inflation tube) and myringotomy, and in approximately half of the patients, a tympanostomy tube was inserted. The patients had sometimes been given oral antibiotics or steroids when the middle ear condition worsened.

Topical Instillation of Triamcinolone Acetonide

In patients without eardrum perforation, a myringotomy was made, followed by the removal of the viscous MEE, and then triamcinolone acetonide was instilled into the middle ear cavity. In cases with persistent perforation, triamcinolone acetonide suspension (concentration, 40 mg/mL) was applied via the eardrum perforation after the removal of MEE or otorrhea. Then, the triamcinolone acetonide was expelled through the eustachian tube by applying a positive pressure using a pneumatic otoscope. The patients were asked not to swallow their saliva when the suspension reached the pharynx. In cases with granulation tissue formation, the granulation of the mesotympanum was removed via the eardrum perforation using a cutting forceps (Gruenwald

oval punchers for ear surgery) as much as possible, and the above procedure was performed. Without any anesthesia, patients rarely complained of pain or discomfort. Bleeding was easily controlled by the application of cotton balls soaked with epinephrine. All procedures were performed under an operating microscope. Severe cases needed induction therapy, that is, the instillation was repeated once a week, up to a maximum of 5 times, until the middle ear condition improved. Twenty milligrams of triamcinolone acetonide was prepared for the treatment of each ear. By suctioning and discarding with saliva, presumably less than 5 mg of the suspension remained in the middle ear for each treatment. The patients were monitored continuously, and triamcinolone acetonide was again administered into the middle ear by the same procedure when MEE or otorrhea recurred. In the control group, the patients with OME underwent myringotomy or insertion of tympanostomy tubes and were given eardrops that contained betamethasone (concentration, 1 mg/mL) for instillation twice daily for 1 to 2 weeks. For draining ears, patients were asked to use eardrops that contained betamethasone twice daily until otorrhea stopped. Some of the control patients took oral steroids when the otorrhea was uncontrollable or when a deterioration in the bone conduction threshold was observed. The patients of both groups continued to take several kinds of drugs, such as theophylline, β -stimulants, carbocysteine, and leukotriene receptor antagonists, prescribed by respiratory physicians during the treatment. Topical or systemic administration of antibiotics was added when otorrhea was highly infected.

Evaluation of Therapy Efficacy

By otomicroscopic findings, the efficacy of the therapy was determined by the length of the period without MEE or otorrhea at the end point of the study and was classified into 1 of 4 categories: excellent, without MEE or otorrhea for more than 3 months; good, for 3 weeks to 3 months; fair, within 3 weeks; or poor, no resolution.

Evaluation of Hearing

The air and bone conduction hearing levels of the patients were evaluated by pure tone audiometry before and at the end point of the study. For the audiometric results at the end point of the study, the latest audiogram was used for each patient. When the hearing threshold of a patient at each frequency was beyond the measurement limit of the audiometer, the

measurable level plus 5 dB was defined as the hearing level of the patient at that frequency.

Middle Ear Mucosa Abnormalities and Culture Results

To analyze the efficacy of the therapy using triamcinolone acetonide, the middle ear mucosa abnormalities just before therapy in the triamcinolone acetonide group were classified into 1 of the following 4 categories: grade 1, almost normal or slightly edematous; grade 2, edematous and slightly thickened; grade 3, highly edematous and thickened; or grade 4, highly thickened or with granulation tissue formation. In addition, the culturing of MEE or otorrhea was performed to detect microorganisms and fungi by a routine laboratory isolation. Informed consent was obtained from all the patients.

Statistical Analysis

Statistical analysis was performed using the paired *t* test or χ^2 test. Two-tailed *P* < .05 was considered statistically significant.

RESULTS

Otomicroscopic Findings

Table 2 gives the otomicroscopic findings of the ears in the 2 groups. Before the therapy, 18 ears showed MEE, and 23 ears had various sized eardrum perforations with otorrhea. At the end point of the study, 17 ears had an intact eardrum without MEE. However, 26 ears had persistent eardrum perforation. In the control group, OME was not resolved in 10 ears and only 2 ears showed intact eardrums. On the basis of these criteria, the efficacy of the therapy for 43 ears was determined as indicated in Table 3. Thirty-five ears (81%) were judged as excellent or good responders to the therapy. On the contrary, there was no effect on persistent otorrhea from medium to large perforations in 3 ears, which were judged as poor responders. In the control group, 7 ears (26%) were controlled well by the eardrops that contained betamethasone, whereas the remaining 20 ears had frequent recurrence of MEE or otorrhea. The efficacy of the therapy in the triamcinolone acetonide group was significantly higher than that in the control group (*P* < .001).

Hearing Results

The average air and bone conduction hearing levels at each frequency of the ears in the triamcinolone acetonide groups are

Table 3. Efficacy of the Therapy Judged by Period Without Middle Ear Effusion or Otorrhea

Criteria*	No. (%) of ears†	
	Triamcinolone acetonide group	Control group
Excellent	20 (46)	2 (7)
Good	15 (35)	5 (19)
Fair	5 (11)	6 (22)
Poor	3 (7)	14 (52)

*Excellent indicates without middle ear effusion or otorrhea for more than 3 months; good, between 3 weeks and 3 months; fair, less than 3 weeks; and poor, no response.

†*P* < .001

given in Table 4. The air conduction hearing level at 1,000 Hz and the average hearing level in the speech frequency range at the end point of the study were significantly improved compared with those before the therapy. The mean bone conduction hearing level was almost the same before and at the end point of the study, except at the frequency of 250 Hz. None of the ears showed signs of deafness during the therapy. All patients, except one who had been given oral prednisolone daily because of severe bronchial asthma, showed serum cortisol levels within the normal range during the therapy.

The hearing results of 27 ears in the control group are given in Table 5. At 4,000 Hz, the bone conduction hearing level at the end point of the study significantly deteriorated compared with that before therapy. One male patient showed unilaterally progressive sensorineural hearing loss, resulting in profound conductive deafness. Although the air conduction hearing levels worsened after the therapy at all frequencies except at 1,000 Hz, the difference before and at the end point was not statistically significant at any frequencies. The hearing gains at each frequency after the therapy in the triamcinolone acetonide group and in the control group are given in Table 6. The ears of the triamcinolone acetonide group showed hearing gains at several frequencies in bone and air conduction, whereas the ears of the control group failed to show any hearing gains at any frequencies at the end point of the study. In particular, the hearing gains of bone conduction at 2,000 Hz and 4,000 Hz were significantly larger in the triamcinolone acetonide group than in the control group.

Table 2. Otomicroscopic Findings of Patients Before and at the End Point of Therapy

Findings	Triamcinolone acetonide group (n = 43), No.		Control group (n = 27), No.	
	Before	End point	Before	End point
Otitis media with effusion	18	0	11	10
Eardrum perforation	23	26	9	13
Large*	5 (4)	4 (1)	1 (1)	4 (3)
Medium*	7 (2)	9 (2)	5	7 (3)
Small	11	13	3	3
Tympanostomy tube	2	0	4	2
Intact	0	17	3	2

*Numbers in parentheses are the number of ears with granulation tissue formation.

Table 4. Hearing Results of Patients in Triamcinolone Acetonide Group (n = 43 ears)

Frequency, Hz	Bone conduction HL, dB		Air conduction HL, dB		P value
	Before	End point	Before	End point	
125			36 ± 17	46 ± 32	
250	11 ± 8*	18 ± 11*	39 ± 16	39 ± 18	<.01
500	14 ± 9	17 ± 12	36 ± 13	33 ± 16	
1,000	14 ± 10	13 ± 13	39 ± 16*	32 ± 17*	<.05
2,000	27 ± 15	24 ± 13	45 ± 19	41 ± 20	
4,000	34 ± 18	32 ± 19	53 ± 26	51 ± 30	
8,000			66 ± 24	71 ± 23	
Average in speech	18 ± 11	18 ± 13	40 ± 16*	36 ± 18*	<.05

Abbreviation: HL, hearing loss.

*Frequency range.

Table 5. Hearing Results of Patients in Control Group (n = 27 ears)

Frequency, Hz	Bone conduction HL, dB		Air conduction HL, dB		P value
	Before	After	Before	After	
125			35 ± 14	37 ± 17	
250	9 ± 10	14 ± 10	36 ± 14	41 ± 19	
500	13 ± 10	17 ± 12	34 ± 12	38 ± 22	
1,000	10 ± 10	12 ± 13	36 ± 15	36 ± 23	
2,000	21 ± 12	25 ± 16	41 ± 16	42 ± 22	
4,000	24 ± 16*	34 ± 19*	47 ± 16	53 ± 29	<.05
8,000			63 ± 25	69 ± 29	
Average in speech	14 ± 10	18 ± 13	37 ± 13	39 ± 22	

Abbreviation: HL, hearing loss.

*Frequency range.

Table 6. Hearing Gain of Ears in Triamcinolone Acetonide Group (n = 43) and Control Group (n = 27)

Frequency, Hz	Bone conduction HL, dB		Air conduction HL, dB		P value
	Triamcinolone acetonide group	Control group	Triamcinolone acetonide group	Control group	
125			-5 ± 20	-3 ± 24	
250	-7 ± 15	-5 ± 10	1 ± 20	-4 ± 23	
500	-3 ± 10	-4 ± 12	3 ± 14	-3 ± 26	
1,000	0 ± 11	-2 ± 12	7 ± 16	0 ± 26	
2,000	3 ± 13*	-5 ± 15*	4 ± 16	-1 ± 24	.05
4,000	2 ± 10*	-9 ± 17*	2 ± 21	-5 ± 27	.05
8,000			-5 ± 23	-6 ± 27	
Average in speech	0 ± 9	-4 ± 13	4 ± 14	-1 ± 25	

Abbreviation: HL, hearing loss.

*Frequency range.

Efficacy of Triamcinolone Acetonide Therapy and Clinical Factors

Correlation between the efficacy of the instillation of triamcinolone acetonide therapy and the abnormalities of the middle ear mucosa was analyzed as shown in Figure 1. In excellent responders, the pathologic change of the middle ear mucosa was relatively small. However, 3 nonresponders showed grade 3 or grade 4 pathologic changes of the middle ear mucosa. The pathologic change of the middle ear mucosa significantly influenced the efficacy of the therapy ($P <$

.001). The culturing results for bacteria and fungi in the triamcinolone acetonide group are given in Table 7. Before the therapy, microorganisms were detected from unilateral or bilateral ears of 16 patients. The most frequent pathogen isolated from the ears was *Staphylococcus aureus*, followed by *Pseudomonas aeruginosa*. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection was identified in 2 ears. All but one of the ears infected by these pathogens had an eardrum perforation with persistent otorrhea. MEE or the otorrhea of 8 patients were culture negative.

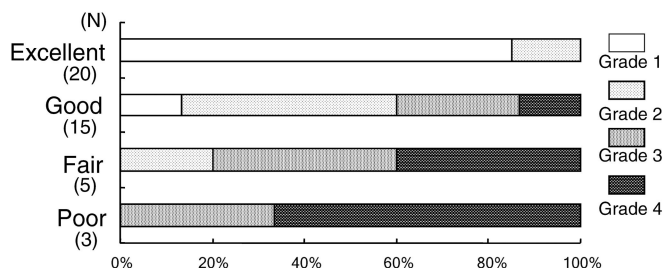


Figure 1. Efficacy of instillation of triamcinolone acetonide and pathologic changes in middle ear mucosa. Grade 1 indicates almost normal or slightly edematous; grade 2, edematous and slightly thickened; grade 3, highly edematous and thickened; and grade 4, highly thickened or with granulation tissue formation.

Table 7. Culture Results of Middle Ear Effusion or Otorrhea in 24 Patients in the Triamcinolone Acetonide Group

Culture	No. of patients*
Positive for bacteria	16
<i>Staphylococcus aureus</i>	6
<i>Pseudomonas aeruginosa</i>	3
MRSA	2
PRSP	1
<i>Corynebacterium</i>	3
CNS	5 (1)
Others	2
Negative for bacteria	8 (3)
Positive for fungi†	3
Negative for fungi	21 (4)

Abbreviations: CNS, collagenase-negative *Staphylococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; PRSP, penicillin-resistant *Streptococcus pneumoniae*.

*Numbers in parentheses are the culture results in middle ear effusion from the patients without eardrum perforation.

†*Candida albicans*, *Aspergillus*, and yeast-like cells.

Fungi were rarely detected from MEE or otorrhea, and *Candida albicans*, *Aspergillus*, and yeast-like cells were recovered from only 3 patients. Two of these patients had frequently been administered systemic steroids for asthmatic attacks. The therapy significantly reduced persistent otorrhea, resulting in a decrease in the number of pathogen-positive ears. Although 2 ears infected with MRSA before the therapy were successfully treated using triamcinolone acetonide and systemic administration of antibiotics susceptible for MRSA, MRSA was newly isolated from one ear during the therapy, and this patient was judged as a poor responder to therapy. From the other 2 poor responders, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were detected from their otorrhea.

DISCUSSION

The presence of eosinophilic inflammation has been well established not only in the lower airways but also in the upper airways of patients with bronchial asthma. Indeed, rhinosinusitis with nasal polyposis or nasal allergy is frequently

associated with bronchial asthma.⁷ OME or chronic otitis media is sometimes found in asthmatic patients and has been called EOM. EOM is not as rare a condition in asthmatic patients as was previously believed. Recently, the clinical surveillance of EOM has been performed in the ENT departments of major hospitals all over Japan, and 341 patients have been diagnosed as having definite cases of EOM according to the criteria reported.³ Therefore, it is expected that a sizable population of asthmatic patients will be diagnosed as having this disease if it is properly recognized. Indeed, Haruna et al⁸ reported that the occurrence of EOM is extremely high in patients with aspirin-intolerant asthma. Currently, it is generally accepted that one of the most effective treatments for eosinophilic inflammation is the administration of a steroid.^{9–11} In this study, we instilled triamcinolone acetonide into 43 ears with EOM and evaluated the efficacy of the therapy and compared it with that of a conventional treatment using eardrops that contained betamethasone. Triamcinolone acetonide is a steroid suspension with a medium length half-life. It may take longer to be effective because the suspension is drained from the middle ear by a mucociliary transport system compared with most other water-soluble steroids, such as betamethasone, which are applied to the middle ear.

Recently, we have reported that the mucosa of the middle ear and the eustachian tube is a shock organ for antigenic materials to induce eosinophilic inflammation.⁶ To control EOM, it seems important to treat both lesions. Therefore, we also instilled triamcinolone acetonide in the mesotympanum through the eardrum perforation and expelled it into the eustachian tube. The patients of the control group had been treated with eardrops that contained betamethasone, a water-soluble steroid with a long half-life. However, the therapy showed poor outcome. The difference may be because triamcinolone acetonide stays longer in the middle ear than betamethasone and the fact that we treated both the mesotympanum and eustachian tube. In our immunohistological study of triamcinolone acetonide applied to the middle ear mucosa, the number of infiltrating cells, including eosinophils, and the number of immunoreactive cells for eosinophil chemoattractants markedly decreased, whereas the number of apoptotic cells significantly increased.¹²

In our results, the efficacy of the therapy using triamcinolone acetonide was 81%, which appears to be far higher than that in the control group. However, the abnormalities of the middle ear mucosa markedly influenced the efficacy of the therapy. That is, the ears with a highly granulated or thickened middle ear mucosa responded poorly to the therapy. This is because in such ears there is little space in the mesotympanum for the instillation of triamcinolone acetonide, and it is often difficult to drain the suspension applied in the mesotympanum to the nasopharynx through the eustachian tube.

The other important factor related to the efficacy of the therapy was the presence of bacterial infection of the middle ear. In particular, ears with MRSA and *Pseudomonas* infections hardly responded to the present therapy. Before the triamcinolone acetonide instillation treatment, oral or intra-

venous administration of antibiotics is needed to eradicate pathogenic bacteria. In this study, more than one third of the treated ears returned to normal otoscopic conditions. Eosinophilic inflammation of the respiratory tract is long lasting and needs continuous treatment, and repeated instillation of triamcinolone acetonide is necessary when EOM recurs.

Surprisingly, in the results from the recent surveillance of EOM in Japan, approximately half of the patients showed deterioration in the bone conduction hearing threshold, and among these patients, 6% became completely deaf.³ In contrast, our study showed that the incidence of this deterioration in the patients treated with triamcinolone acetonide was minimal, whereas one ear of the control group showed profound sensorineural hearing loss unilaterally. When we studied the air conduction threshold at the speech frequency range, the average threshold was significantly improved at the end point of the study in the triamcinolone acetonide group. When comparing the results between the triamcinolone acetonide group and the control group, the average bone conduction hearing levels at high frequencies in the control group significantly deteriorated compared with those in the triamcinolone acetonide group. Although we applied positive pressure to the ears to drain the suspension to the eustachian tube, none of the patients complained of dizziness or hearing loss during the procedure. Therefore, as far as the hearing results are concerned, the instillation of triamcinolone acetonide seems to be safe and satisfactory.

The cause of the sensorineural hearing loss associated with EOM has not been determined. High levels of toxic substances of eosinophilic inflammation, such as eosinophilic cationic protein, or inflammatory cytokines, such as interleukin 5, have been detected in MEEs.^{12–14} These substances can easily pass through the round window membrane to cause inner ear damage.¹⁵ If a bacterial infection is associated with EOM, bacterial toxins also pass through the round window membrane and damage the structures of the inner ear.^{16,17} In addition, vasculitis of the inner ear caused by eosinophils may be one of the pathogenic mechanisms of inner ear damage.

The present results suggest that the instillation of triamcinolone acetonide into the mesotympanum and eustachian tube is effective for patients with EOM regarding the control of MEE or otorrhea and hearing. To obtain a good response to the therapy, it is important to eliminate bacterial infections and to remove any granulation tissue or highly thickened mucosa of the middle ear to create enough space for the instillation of triamcinolone acetonide and the drainage to the eustachian tube before therapy.

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