Original Article

A comparison of different treatment modalities used as otorrhea prophylaxis following ventilation tube placement

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ABSTRACT

Objectives: This study aims to compare the efficacy and complications of different medical treatment modalities used to prevent otorrhea following ventilation tube placement.

Patients and Methods: This single-center, evaluator-blinded, controlled study included a total of 241 consecutive children (137 males, 104 females; mean age: 7.3±2.6 years; range, 3 to 13 years) who underwent bilateral ventilation tube placement due to bilateral serous otitis media between July 2014 and June 2016. The patients were classified according to the medical treatment protocols applied. Group 1 (n=56) received oral antibiotics; Group 2 (n=57) received oral antibiotics + local antibiotic ear drops; Group 3 (n=65) received local antibiotic ear drops; and Group 4 (n=63) received local antibiotic-glucocorticoid ear drops.

Results: The lowest rate of otorrhea seen was 5.2% in Group 2, followed by 6.34% in Group 4. The highest rate of otorrhea was seen in Group 1. In the evaluation of the efficacy of the treatments, otorrhea was eliminated in Group 2 at a rate of 75% on Day 4. The same success rate was reached on Day 6 in Group 4 and on Day 12 in the other groups. The highest rate (28%) of side effects was seen in Group 2. Although the rates in the groups applied with local treatments were lower than those of the other groups, the difference was not statistically significant (p=0.051).

Conclusion: The administration of local antibiotic-glucocorticoid ear drops can be considered an effective and safe treatment option with similar otorrhea and lower complication rates.

Keywords: Antibiotic ear drops, oral antibiotic, serous otitis media, steroid ear drops, ventilation tube placement.

The most frequent surgical procedure applied under general anesthesia to pediatric patients is the insertion of a ventilation tube (VT) to patients with serous otitis media. The leading complication that can develop in patients applied with a tube placement is early otorrhea emerging in approximately the second week.[1] Although the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) recommends the use of topical antibiotic or antibiotic/steroid combinations without oral antibiotic treatment to reduce the occurrence of early postoperative otorrhea, no consensus has yet been reached on the most appropriate treatment.[2,3] In a recent study, the use of oral antibiotics to reduce the occurrence of early postoperative otorrhea

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was reported by 54% of pediatric emergency physicians, and 9% of pediatric ear, nose and throat (ENT) specialists.[4]

The ideal treatment should be one that is easy for the patient to use, has a low complication rate, low-cost, and low recurrence rate. The main goal of researchers in this area is to develop the most effective treatment methods leading to the least harm to the patient.[1,5] Therefore, there are studies in the literature comparing the use of different treatment modalities such as oral antibiotics, local antibiotics + steroids, and local antibiotics.[1-5] The aim of those studies has been the eradication of microorganisms which can colonize the orpharyngeal or external canal.[6] Authors advocating the use of local antibiotics and steroids have reported that the use of these agents allows a minimal inhibitor concentration to be reached more quickly than systemic treatment of the middle ear and outer ear, and by changing the pH of the middle ear, the environment suitable for the microorganisms to live and thrive is destroyed.

It has also been emphasized that the use of oral antibiotics has potential side effects on renal, gastrointestinal, and hepatic functions.[2-7] The authors supporting the use of oral antibiotics have taken a distant approach to studies made with fluoroquinolone group antibiotics in respect of ototoxicity.[8-13] This is based on the fact that in animal studies, the tympanic membrane has been perforated iatrogenically, and as the inflammatory process in these animals is different from that of humans, and as no mucosal inflammation or various pro-inflammatory and anti-inflammatory cytokines have been found, these experiments do not fully reflect the disease environment.[8] Furthermore, some authors have reported that there may be tube obstruction due to the high viscosity of combined treatment forms, particularly local treatments with steroids, which can contribute to otorrhea.[13]

In the present study, we aimed to compare the efficacy and complications of different medical treatment modalities routinely used to prevent otorrhea following VT placement and to identify the most effective and safest treatment modality.

PATIENTS AND METHODS

This single-center, evaluator-blinded, controlled study was conducted at Department of Otorhinolaryngology, Ahi Evran University Training and Research Hospital between July 2014 and June 2016. A bilateral VT was inserted to a total of 241 consecutive pediatric patients (137 males, 104 females; mean age: 7.3±2.6 years; range, 3 to 13 years) with the diagnosis of bilateral serous otitis. To avoid any medicolegal problems that could arise after the treatment, the groups were not randomized; however, the treatment protocols and possible complications were explained to the patient and their family and they were left free to select the postoperative antibiotic protocol. To protect group homogeneity in respect of the rates of postoperative otorrhea without affecting the reliability of the study, patients aged <3 years or >13 years, having a history of VT placement, and having recurrence, or previous adenoidectomy or tonsillectomy were excluded from the study, as outliers could occur in the pressure and compliance values of tympanometric measurements. Those who had a cleft palate, Down's syndrome, cystic fibrosis, impaired mucociliary activity or any disease that could constitute a risk factor for the development of otorrhea such as immune failure, or a known allergy to any of the agents used in the treatment were also excluded. A written informed consent was obtained from each parent and/or legal guardian of the patient. The study protocol was approved by the Ankara Training and Research Hospital Ethics Committee (approval dated 05/03/2014, session number 0539 (HNEAH-KAEK 2014), decision number: 4505). The study was conducted in accordance with the principles of the Helsinki Declaration.

For each of the patients to be operated for bilateral serous otitis media, a record was made preoperatively including age, sex, previous antibiotic use, and type and history of acute middle ear inflammation. Preoperative measurements were taken with a MAICO MI44 tympanometer (Maico Diagnostic GmbH, Berlin, Germany). The pressure value was recorded as daPA and the compliance value as mL.

Patients included in the study were those with VT inserted due to serous otitis media

with at least one of the following conditions: no appropriate response to antibiotic treatment applied, conduction type hearing loss ongoing for longer than eight weeks and positive tympanometric findings due to effusion (Jerger classification B type), or more than six episodes of acute otitis media within the last six months. The procedure can be summarized as disinfection of the auricle and external ear canal with povidone-iodine solution, then parasynthesis inserted to the anterior inferior quadrant of the tympanic membrane under microscopy and the insertion of a Shepard VT to the glue ear.

To minimize factors that could cause tube obstruction, all the surgical procedures were performed by a single surgeon using the same surgical technique and the same type of VT. Thus, it was aimed to make an optimal evaluation of the effect of the antibiotic treatment protocol on tube obstruction and otorrhea. During the follow-up period, the patients who reported that the discharge discontinued were visited at home and the presence of obstruction was objectively evaluated by checking the tube otoscopically.

The parents of the patients were informed by the clinician performing the surgical procedure about the medical treatment methods that are routinely used and, to avoid any medicolegal problems that could arise due to complications that could develop after the treatment, the choice of treatment was based on voluntary basis. The patients in the study were grouped according to the treatments applied.

Group 1 (n=56) received oral antibiotics and anti-inflammatories (amoxicillin + clavulanic acid + ibuprofen); Group 2 (n=57) received oral antibiotics (amoxicillin + clavulanic acid) + local antibiotic ear drops (ofloxacin); Group 3 (n=65) received local antibiotic ear drops (ofloxacin); and Group 4 (n=63) received local antibiotic-glucocorticoid ear drops (ciprofloxacin hydrochloride + dexamethasone sodium phosphate) (Figure 1).

In patients with mucoid fluid, aspiration was applied before placement of the tube in the glue ear. Topical treatments were started after discharge of the patients.

For a period of four weeks postoperatively, the patients were evaluated for early development of otorrhea. The author who applied the surgical procedure and organized the medical treatment did not participate in the postoperative follow-up of the study. The postoperative follow-up examinations were applied and the data recorded by a different author and coding was used to avoid bias in the follow-up and statistical stages. In the follow-up protocol, a telephone call was made to the parents of the patients once every two days and they were asked about otorrhea. In addition, the parents completed the Child Health Questionnaire (CHQ), which measures quality of life related to general health, and the Otitis Media-6 (OM-6) Questionnaire, which measures quality of life related to disease-specific health.

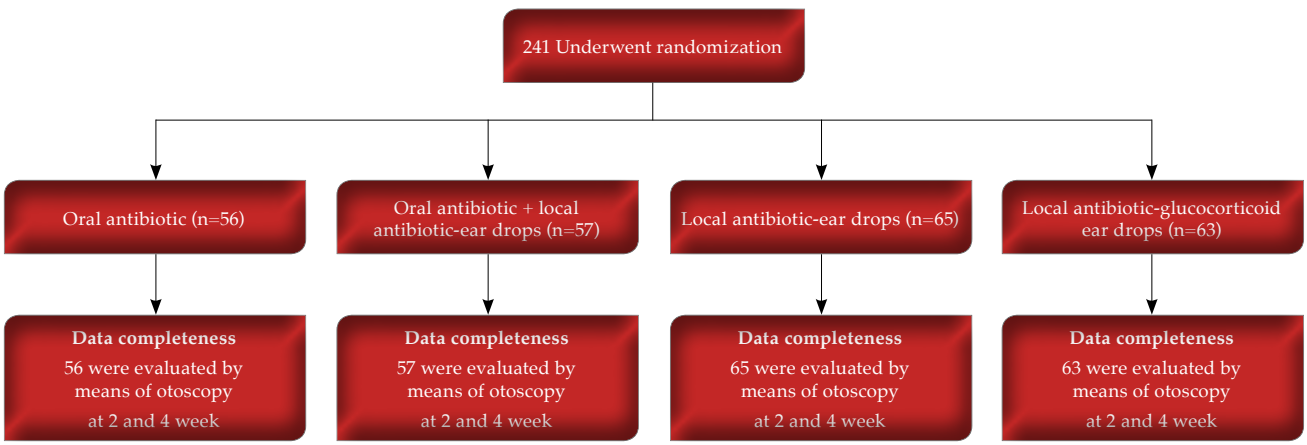

Figure 1. Study flow chart.

Patients who in whom otorrhea stopped were visited at home by a single physician and were evaluated in respect of tube obstruction. The patients who had tube obstruction used 0.3% ciprofloxacin hydrochloride drops three times a day for one week and, at the end of the week, the tube was cleared with aspiration in the clinic.

Statistical analysis

The study power and sample size calculation were performed using the G*Power version 3.1.9.2 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The rate of postoperative otorrhea was assumed taking into consideration the rates of otorrhea seen in study groups of similar studies (oral antibiotic treatment 20%, local antibiotic-glucocorticoid ear drops 8%) and it was predicted that with 55 patients in each group, the difference between the treatments would be determined with 96% power.

Statistical analysis was performed using the PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test and variance homogeneity with the Levene test. Quantitative data were expressed in mean ± standard deviation (SD) and median (min-max), while categorical data were expressed in number and percentage. For multiple groups, one-way analysis of variance (ANOVA) was used, while the Tukey Honestly Significant Difference (HDS) test was used for inter-group comparisons. To determine the presence of otorrhea, the success of the treatment process and the duration of the otorrhea episode in the different treatment groups according to the diaries of the parents and the otoscopic examinations, Kaplan-Meier curves were drawn and the differences between groups were evaluated with the log-rank test.

RESULTS

No statistically significant difference was found between the age and sex values of the patients (p=0.209 and p=0.453). No statistically significant difference was observed among the groups in terms respect of preoperative pressure (daPA) and compliance (mL) values in both ears (p>0.05 for all). The demographic data

Table 1. Baseline demographic data and tympanometric measurement results of the groups and the rates of otorrhea development during follow-up

	Oral antibiotic (n=56)			Oral antibiotic + local antibiotic ear drops (n=57)			Local antibiotic ear drops (n=65)			Local antibiotic-glucocorticoid ear drops (n=63)			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			7.8±2.5			7.1±2.4			6.9±2.4			7.5±2.7	0.209
Sex													0.453
Male	30			36			37			42			
Female	26			21			28			21			
Right ear pressure			-313.7±76.4			-302.8±71.7			-291.7±51.4			-301.1±73.1	0.374
Right ear compliance			0.4±0.2			0.4±0.2			0.5±0.2			0.4±0.2	0.774
Left ear pressure			-293.7±77.1			-300.9±64.1			-291.5±59.3			-293.6±61.5	0.873
Left ear compliance			0.5±0.2			0.4±0.1			0.4±0.2			0.5±0.2	0.293
Otorrhea at 4 week of follow-up	11	19.64		3	5.26		6	9.23		4	6.34		0.041

SD: Standard deviation; One-Way ANOVA (with Tukey HSD).

and tympanometric measurement results of the patients are shown in Table 1. At the end of the four-week follow-up period, the lowest rates of otorrhea were seen in the oral antibiotic + local antibiotic ear drops at a rate of 5.26% and in the local antibiotic-glucocorticoid ear drops group at a rate of 6.34%. According to the evaluation between the two groups in respect of otorrhea, there was no significant difference (p=0.997). In both groups, the difference compared to the oral antibiotic group was significant (p<0.05 for both). At the end of the four-week follow-up period, otorrhea was seen in the local antibiotic ear drops group in 9.23% of patients. Compared to the other groups, the difference was not statistically significant (p>0.05 for all). In the evaluation of the treatment efficacy, otorrhea was completely eliminated at a mean time of four days in 75% of the oral + local antibiotic group. The same success rate was achieved on Day 6 in the local antibiotic + steroid combination group and on Day 12 in the other groups. The relationships between time and the rates of otorrhea according to the treatments applied are shown in Figure 2.

According to the evaluation of side effects, no side effect was seen in any patient requiring discontinuation of the drug treatment. The

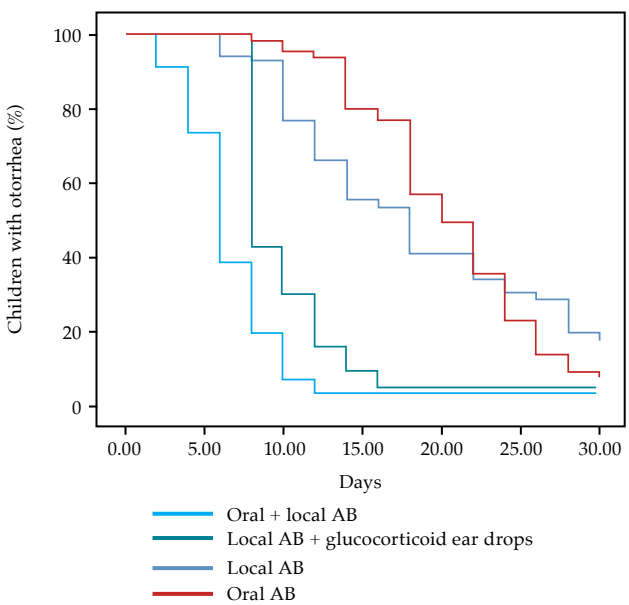

Figure 2. Kaplan-Meier plot showing treatment efficacy during the 30-day follow-up period.

Table 2. Rates of side effects seen during treatment according to the groups

	Oral antibiotic (n=56)		Oral antibiotic + local antibiotic ear drops (n=57)		Local antibiotic ear drops (n=65)		Local antibiotic-glucocorticoid ear drops (n=63)		*p*
	n	%	n	%	n	%	n	%	
Side-effects seen during the 4-week follow-up period	9	16.1	13	22.8	5	7.7	7	11.1	0.051
Pain or sensitivity during local use	0	0.0	2	3.5	4	6.15	6	9.5	0.081
Gastrointestinal side-effects	6	10.7	8	14.05	0	0.0	0	0.0	0.001
Liver toxicity	0	0.0	0	0	0	0.0	0	0.0	
Allergic skin reaction	3	5.4	3	5.25	1	1.55	1	1.6	0.356
Tube obstruction	1	1.78	3	5.25	3	4.61	4	6.34	0.678

Chi-square test (Monte Carlo).

highest rate of total side effects was in the oral antibiotic + local antibiotic ear drops group (22.8%), and the side effect rates of the local treatment groups were lower than those of the other groups, although it did not reach statistical significance (p=0.051). The treatment protocols and rates of side effects seen are shown in Table 2. Considering tube obstruction, although there was an increased rate of tube obstruction in the groups applied with local treatment, the difference was not statistically significant (p=0.678) (Table 2).

DISCUSSION

Early postoperative otorrhea is one of the most frequently seen complications occurring after VT placement.[1,2] Despite the AAO-HNS recommendation to use topical antibiotic drops without oral antibiotic treatment[3] and the virtually standardized treatment approach of ENT specialists, the treatment approach to otorrhea patients, who are frequently seen by different specialist branches, shows an extremely wide spectrum from oral antibiotic use to topical antibiotic + steroid combinations.[4] In the current study, we compared the efficacy and complication rates of different medical treatment modalities which are routinely used to prevent otorrhea following the placement of VT. In our study, no statistically significant difference was found between the groups.

In this study, two different groups received oral antibiotic treatment. The first of these was oral antibiotic treatment only, which, as stated by Badalyan et al.[4] in a study evaluating the preventative effect against the development of otorrhea, is still the first choice of most emergency pediatric specialists in the treatment of otorrhea. Kocatürk et al.[14] applied VT treatment to 280 patients over a four-year period and evaluated the development of otorrhea. The patients were grouped according to treatments as a control group, isotonic saline, oral antibiotics (25 mg/kg ampicillin/sulbactam combination), and topical antibiotic drops (ofloxacin otic drops) groups and a significantly low rate of otorrhea was seen in all the treatment groups, compared to the control group (p<0.05). In the treatment groups, otorrhea was seen in the oral antibiotic group at a rate of 14.3%, and the lowest rate of 8.57% was seen in the topical antibiotic drops group; however, there was no significant difference between the groups in respect of otorrhea development. In a recent literature review, otorrhea rates in patients using ear drops containing ciprofloxacin (10 to 23%) had significantly lower than the rates in patients using oral antibiotics (20 to 70%).[15] In the current study, the otorrhea rate in the oral antibiotic group was 19.64%, consistent with literature. Another group in the current study in which oral antibiotics were used was the oral antibiotic + local antibiotic ear drops group. Although this patient group had the lowest rate of otorrhea in this study, there was no statistically significant difference in comparison with the groups in which local administration was used (p>0.05).

In the current study, there were two groups where topical treatment was applied without oral antibiotic use. In one of these groups, only local ofloxacin was used and in the other, ciprofloxacin hydrochloride was used in combination with dexamethasone sodium phosphate. There are many studies in the literature comparing these two treatment modalities with each other and with oral antibiotic treatment.[1-9] In a recent study by Samarei,[8] the effect of local treatment agents on the development of otorrhea was examined, and otorrhea was seen at a rate of 8.2% with the use of ofloxacin drops as the local antibiotic agent. The authors emphasized that the difference between this rate and the rate of 5.2% in the ciprofloxacin and dexamethasone group was not significant (p=0.21).

Furthermore, Heslop et al.[16] compared topical antibiotics, saline irrigation and oral antibiotic treatments and reported treatment failure in 23% of the patients applied with topical antibiotics, and this rate reached 70% in the oral antibiotic group. Another study reported that otorrhea was seen in only 5% of patients in a two-week follow-up of local antibiotic + glucocorticoid combination treatment, while the rate was 44% in the oral antibiotic group.[17] In the current study, otorrhea was seen in 6.34% in the local antibiotic + glucocorticoid combination group which was similar to the lowest rate of the oral antibiotic + local antibiotic ear drops group.

One of the groups in the current study was treated with a combination of ciprofloxacin

and dexamethasone. Although this caused heterogeneity in the study groups, there are different views related to the efficacy of local antibiotic treatments. The emphasis in a recent Cochrane analysis[18] that evidence values were low in studies which compared different topical antibiotics, and that it was difficult to make a decision based on these studies, made it necessary to form this group in the current research. It has been shown in the literature that ofloxacin ear drops are more effective than ciprofloxacin in the treatment of otorrhea, and the combination of ciprofloxacin and steroids has been shown to more effectively significantly reduce the development of postoperative complications in patients with tube placement.[1,10] However, the fact that those studies were supported by the industry is an important limitation that must be taken into consideration while interpreting the results. Similarly, a recent study reported a significant difference in the incidence of otorrhea and tube obstruction between patients administered antibiotic/steroid ear drops preoperatively and patients administered ear drops without steroids.[5] Considering the results of the current study, the best results of the groups with local treatments were in the ciprofloxacin/dexamethasone combination group showed that the results were similar to those of the studies by Giles et al.[1] and Roland et al.[10] The main reason for this can be attributed to normalization of the immune response by the steroid treatment preventing excessive cytokine expression. Recent literature has recommended the addition of steroid agents in conditions where the inflammatory process is suppressed, including in cases with severe sepsis.[19]

More intriguingly, evaluation was made of the days from when treatment started to when otorrhea stopped in the current study. In the oral antibiotic + local antibiotic ear drops group, episodes of otorrhea completely eliminated in 75% of the patients by the mean of Day 4, and the same success rate was achieved on Day 6 in the local antibiotic-glucocorticoid group. No significant difference was seen between these two groups in respect of the duration of effective treatment. However, the same success rate reached on Day 12 in the groups not applied with combination treatment. Of note, as this subject has not been previously studied in the literature, an accurate comparison with these results cannot be made.

Tube obstruction is one of the complications of VT placement. Various factors have been thought to be responsible in the etiology such as tube diameter, the shedding of epithelial cells, poor surgical technique, and insufficient hemostasis.[20] Although the high viscosity of ear drops containing steroids has been considered to be a cause, there are extremely limited data related to the incidence of tube obstruction associated with ear drops.[13] Samarei[8] compared topical ofloxacin ear drops and ciprofloxacin/dexamethasone combination and reported the tube obstruction rate to be 5.2% in the ofloxacin group and 6% in the ciprofloxacin/dexamethasone combination.

To minimize factors that could cause tube obstruction, all the surgical procedures in the current study were performed by a single surgeon using the same surgical techniques and the same type of VT. Thus, it was aimed to make the optimal evaluation of the effect of the treatment protocols on tube obstruction. In addition, the author who organized the treatment protocols and patient follow-up made home visits to patients who reported by telephone that the discharge stopped, and the presence of tube obstruction was objectively evaluated with otoscopic examination. The lowest rate of tube obstruction was in the oral antibiotic group (1.78%), while the highest rate was in the local antibiotic-glucocorticoid ear drops group (6.34%); however, no statistically significant difference was observed between the groups. These results are also consistent with previous findings in the literature.[8]

The side effect profile of the treatment protocols was evaluated in the current study. No drug side effects were encountered in any patient during the treatment period. In a study by van Dongen et al.[17] the effects of oral antibiotics and antibiotic-glucocorticoid ear drops on the development of otorrhea were evaluated. The most frequently seen side effect was gastrointestinal discomfort in 23% of the oral antibiotic group and in the antibiotic-glucocorticoid ear drops group, local

discomfort or pain in the administration site was reported in 21%. The results of the current study in respect of the side effect profile are consistent with the literature.

A limitation of the current study is that there was no control group or group applied with saline irrigation. In addition, as explained above, the patients and their parents were given information about the treatment protocols and the selection of the treatment was left to them. None of the patients were willing to participate in a control or saline irrigation group and, although both groups were previously studied in the literature, there are insufficient data about the results. Therefore, the absence of these groups in the current study could have had a negative effect on the results. Another limitation of the study is that the grouping was not randomized. However, as can be seen in the demographic data of the patients, there was a highly homogenous distribution of age, sex, and preoperative pressure and compliance values. In the light of these data, the results can be considered not to have been affected by the patient distribution.

In conclusion, our study results showed that although the oral antibiotic + local antibiotic ear drops group had the lowest rate of otorrhea, the side effect profile was high. Therefore, the administration of local antibiotic-glucocorticoid ear drops can be considered an effective and safe treatment option with similar otorrhea and lower complication rates.

Declaration of conflicting interests

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