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ORIGINAL RESEARCH

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Does intraoperative ciprofloxacin-soaked gelfoam have adverse effects on graft success rate? A randomized, double-blind controlled trial

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Abstract

Objectives: The aim of this study was to evaluate whether intraoperative ciprofloxacin-soaked gelfoam is safe in tympanoplasty or not.

Method: In this randomized, double-blind controlled clinical study, we included 100 patients between 18 and 60 years old, having perforation ≥50% of the tympanic membrane and dry ear for at least 2 months who were a candidate for underlay tympanoplasty via postauricular approach. We used ciprofloxacin soaked gelfoam in the case group and betamethasone soaked gelfoam in the control group for packing the middle ear cavity and external auditory canal during their operation. The graft success rate and tympanogram after 6 months follow-up period was considered as the primary outcome. Also, we evaluated the postoperative hearing results 6 months after the surgery as the secondary outcomes.

Results: Postoperative microscopic otoscopy showed a graft success rate of 100% (44/44) and 97.7% (42/43) in the case and control groups, respectively. The level of improvement between the two groups was not significant for air-bone gap (ciprofloxacin: 9.01 ± 7.89 dB, betamethasone 5.31 ± 10.53 dB, $P = .160$), and speech reception thresholds (SRT; ciprofloxacin: 10.23 ± 8.62 dB, betamethasone 7.33 ± 12.60 dB, $P = .260$). 93.2% of all the ears in the case group and 81.4% of those in the control group achieved postoperative air-bone gap within 20 dB, but the difference between them was not significant ($P = .118$).

Conclusions: We found that the application of ciprofloxacin impregnated gelfoam in the middle ear, and the external auditory canal had no adverse effect on the graft success rate in tympanoplasty.

Levels of evidence: 1b.

KEYWORDS
betamethasone, ciprofloxacin, graft success rate, tympanic membrane, tympanoplasty

1 | INTRODUCTION

Chronic supportive otitis media (CSOM) is a common disease.[1] One of the effective methods of treatment of CSOM is surgery. The aim of chronic otitis media (COM) surgery is to maintain an intact tympanic membrane to restore the hearing ability and stop ear discharge.[2]

Although many otologists use postoperative ciprofloxacin drops a few days after COM surgeries, there is increasing concern over its effect on the graft success rate. In some previous studies, the researchers reported both beneficial[3] and adverse[4] effects of postoperative topical antibiotic or steroid drops on tympanic membrane healing. In a study conducted by Orobello et al, it was shown that topical ciprofloxacin 3% drop reduced the fibroblasts and caused a delay in tympanic membrane repair in the rat ear.[5] On the other hand, a study carried out by Wall et al showed that topical ciprofloxacin 0.3% plus dexamethasone 0.1% sterile otic suspension was safe in chronic otitis media surgery.[6]

Gelfoam is usually applied for packing of the middle ear in the underlay graft technique tympanoplasty. Middle ear adhesions or fibrosis following the use of gelfoam were observed.[7] An experimental investigation has described that gelfoam in combination with a corticosteroid reduced middle ear fibrosis.[7] Betamethasone-soaked gelfoam is used routinely for packing the middle ear in tympanoplasty in some centers.[8,9] Similarly, in our center betamethasone-soaked gelfoam has been used for many years as a routine.[10]

Because of the controversy about the adverse effects of ciprofloxacin drop on the graft success rate, more research is required to determine its efficacy and safety in humans.

The aim of this study was to evaluate the safety of intraoperative ciprofloxacin-soaked gelfoam in tympanoplasty and the possible adverse effect on the graft success rate and hearing result.

2 | METHODS AND MATERIALS

2.1 | Trial design

This is a randomized, double-blinded, clinical trial study with a parallel design. Participants were assigned to either intervention or control groups (1:1 allocation ratio). Eligible patients were recruited from January 2019 to July 2019.

The protocol and patient informed consent forms were reviewed and approved by the local Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.643). The study was registered at the Iranian Registry of Clinical Trials (IRCT20200314046773N1; https://www.irct.ir/trial/46563). Participation in this study was completely voluntary. All procedures performed in studies were in accordance with the Helsinki Declaration of 1964. All participants signed the written informed consent before their participation.

2.2 | Participants

Patients were operated in Khalili and Dastgheib hospitals which are affiliated to Shiraz University of Medical Sciences (Shiraz, Iran). These hospitals are tertiary health care centers in the field of otology in southern Iran. All procedures were performed by one academic otologist. The level of expertise was the same.

Inclusion criteria were being 18 to 60 years old, having perforation equal or more than 50% of the size of the tympanic membrane and dry ear for at least 2 months, and not having any systemic illness (lymphoproliferative disease, syphilis, granulomatosis with polyangiitis, and tuberculous otitis media) that needed tympanoplasty for repairing of tympanic membrane perforation.

Exclusion criteria were: (a) simultaneous mastoidectomy, (b) diabetes mellitus, (c) history of immunodeficiency, (d) chronic kidney disease, (e) previous ear surgery, and (f) smoking. Also, all patients who had intraoperative cholesteatoma, granulation tissue, tympanosclerotic plaque, and ossicular erosion were excluded.

2.3 | Interventions

All patients underwent tympanoplasty without mastoidectomy via postauricular approach. After the postauricular incision, the auricle was retracted anteriorly. The rim of perforation was freshened, and then the tympanomeatal flap was elevated along with the posterior annulus to enter the middle ear cavity. After that, the ossicular chain condition and the presence of any pathology were evaluated. The temporalis facia graft was inserted medial to the tympanic membrane remnant and malleus handle as the underlay method.

In the case group, ciprofloxacin (Ciplex eye drops [Ciprofloxacin HCL 0.30% Sina-Daru, Tehran, Iran]) impregnated gelfoam (Gelita-Spon; Gelita Medical, Eberbach, Germany) was placed to fill the middle ear space. After that, the tympanomeatal flap returned to its normal position. The medial part of the external meatus was also packed with ciprofloxacin-soaked gelfoam.

In the control group, the procedure was similar to that used for the case group, with the exception that we used betamethasone soaked Gelfoam (Betamethasone 0.1%, Sina-Daru, Tehran, Iran) in the middle ear cavity and external auditory canal. Betamethasone impregnated Gelfoam has been used as routine for many years in our center for packing the middle ear.[10]

A gauze pack impregnated with ophthalmic tetracycline ointment was placed in the external auditory canal. Then, the posterior auricular incision was closed in two layers. A pressure dressing was applied for the first 24 hours and then changed to a light dressing.

Postoperatively, all patients received oral antibiotics, cephalexin 500 mg every 6 hours for 1 week, but no topical ear drops were given

to them. All patients were visited by the operating surgeon as routine postoperative management. On the other hand, to prevent bias, the other independent academic assessor otolaryngologist reported the postoperative condition in this research. Patients were evaluated by microscopic otoscopy after 1 week when the tetracycline gauze was removed. The follow-up consisted of clinical microscopic otoscopy after 3 weeks for debridement of the external gelfoam and determination of the status of the new tympanic membrane. Then, they were observed within the intervals of the second, third, fourth, and sixth months.

Preoperative and postoperative tympanometry, air conduction (AC), bone conduction (BC), air-bone gap (ABG), and speech reception thresholds (SRT) were measured. A preoperative audiogram was performed 1 week before the surgery, and an audiogram of 6 months after the surgery was selected as a postoperative audiogram. To assess the hearing results, we analyzed pure tone audiometry at frequencies of 0.5, 1, 2, 3, and 4 kHz.

2.4 | Primary and secondary outcomes

An independent academic otolaryngologist, who was blind regarding the type of otic drop, assessed the graft success rate and tympanogram after 6 months follow-up period as a primary outcome. We defined a successful TM graft as an intact TM without retraction, blunting, and lateralization in microscopic ear examination and type A tympanometry in tympanogram. Also, we evaluated the postoperative hearing results 6 months after the surgery as the secondary outcomes.

2.5 | Sample size

For sample size determination, there was no previous clinical trial to compare the ciprofloxacin with betamethasone, therefore, this study was conducted as a pilot study. According to previous studies, considering sample size of more than 40 participants in each study arm is suitable to show a possible significant difference in outcome.[11-13] Therefore, in our study, we considered 40 participants as the ideal sample size for evaluating the effect of ciprofloxacin on graft success rate. By assuming a maximum drop-out rate of 20%, a sample size of 50 patients in each group was considered appropriate.

2.6 | Randomization

Patients were randomly assigned to the case (ciprofloxacin) or control (betamethasone) groups in the random blocks of four subjects. Randomization was done by the blocked randomization method. A computer random number generator generated the sequence of the permuted blocks. Randomization was done by a nurse and only she was aware of the patients' drop.

2.7 | Blinding

Patients, clinical assessors (independent academic otolaryngologist, audiologist), and the statistician who analyzed the data were all blinded to the patients' allocation until the statistical analysis was complete.

2.8 | Statistical methods

Categorical variables were reported as frequency and percentage. Quantitative variables were expressed as mean (±SD). Chi-square or Fisher's exact test was used to evaluate the possible associations among the categorical variables, if appropriate. Parametric and nonparametric continuous variables were analyzed using paired sample *t*-test, independent *t*-test, Mann-Whitney *U* tests, and Wilcoxon, where applicable. *P*-values less than .05 were considered to be statistically significant. The analysis was conducted using SPSS 25 software (SPSS Inc., Chicago, Illinois).

3 | RESULTS

At first, 124 patients were eligible. Twenty-four participants had diabetes mellitus, previous ear surgery, simultaneous mastoidectomy, or declined to participate, so they were excluded. The remaining 100 patients were randomly allocated to two groups by block randomization method according to the type of intraoperative drops (50 patients in each group).

Six patients in the ciprofloxacin group and seven in the betamethasone group were excluded due to loss to follow-up (Figure 1). Although we detected normal graft in the first 4 months, these patients did not meet our inclusion criteria regarding the adequate 6 months follow-up. The two groups were homogeneous regarding the gender and age of the patients (Table 1).

Postoperative microscopic otoscopy revealed a 100% (44/44) graft success rate in the ciprofloxacin group. Otoscopic examination showed small anteroinferior tympanic membrane perforation in one patient in the betamethasone group after 6 months (success rate: 97.7%) (*P*-value = .309).

In all patients with an intact tympanic membrane, tympanometry was in the concordance and reported as type A. The only patient with B-type tympanometry was the one patient in the betamethasone group.

As shown in Table 2, regarding the comparison of preoperative and postoperative variables, the mean BC in the ciprofloxacin group improved statistically although it was not significant clinically. The mean BC in the betamethasone group was not improved significantly ($P = .052$). Mean AC, ABG, and SRT in each group improved both statistically and clinically postoperatively.

In addition, the gains of mean BC, AC, ABG, and SRT between the two groups were also compared. We found significant statistical improvement in BC ($P = .047$) and AC ($P = .007$), but it was not

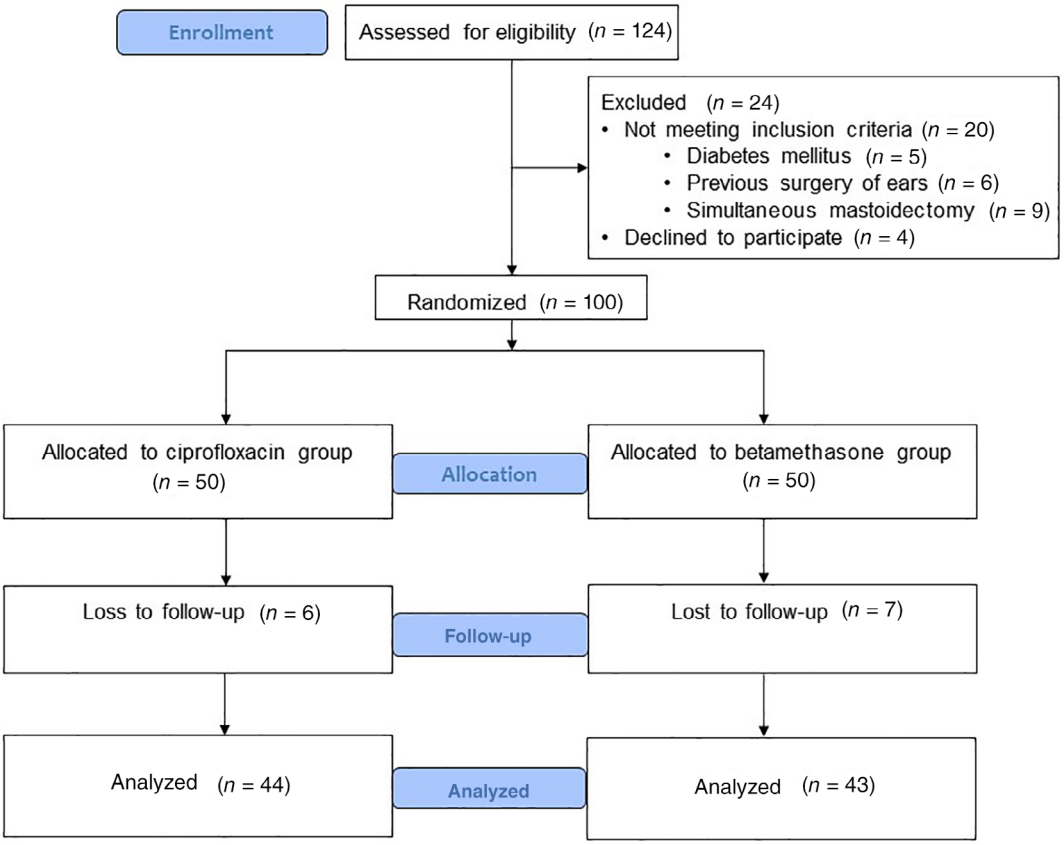

FIGURE 1 CONSORT diagram of the participants

TABLE 1 Baseline characteristics of the patients

Variables	Drug		*P*-value
	Ciprofloxacin	Betamethasone	
Gender			
Male, N (%)	6 (13.6%)	13 (30.2%)	.073[a]
Female, N (%)	38 (86.4%)	30 (69.8%)	
Age, mean (SD)	42.75 (9.56)	41.74 (9.89)	.559[b]

[a]Fisher's exact test.
[b]Mann-Whitney test.

significant clinically. There were no significant differences regarding ABG ($P = .160$) and SRT ($P = .260$) between the two groups.

4 | DISCUSSION

In this prospective double-blind clinical trial, we compared the effect of intraoperative ciprofloxacin vs betamethasone-soaked gelfoam as the control group during tympanoplasty. We found that there was no significant difference between the two groups in terms of graft success rate. The functional and anatomic outcomes did not differ significantly between the two groups.

Previously published studies reported a wide range of graft success rates after tympanoplasty between 64% and 100%.[14-17] In our study, we achieved a graft success rate of 100% in the case (ciprofloxacin) group and 97.7% in the control (betamethasone) group in patients with equal or more than 50% of tympanic membrane perforation.

Ciprofloxacin and ofloxacin are the only antibiotics approved by the United States Food and Drug Administration (USFDA) for prescription in cases with a perforated tympanic membrane. In recent years, topical ciprofloxacin drop has been used widely in otologic diseases, due to the high susceptibility of common microorganisms, especially pseudomonas, and it's very low adverse effects.[18]

Most of the animal studies showed the adverse effect of topical quinolones on the tympanic membrane graft success rate. For instance, in vitro studies reported that topical ciprofloxacin (0.01% or 0.3%) was cytotoxic for the mouse tympanic membrane fibroblasts and reduced the tympanic membrane collagen and a-tubulin protein levels which were exacerbated by steroids.[5,19,20] Also, in the rat model, the quinolone ototopical drops were found to hinder the tympanic membrane healing following tympanoplasty.[18,21,22] In addition, Antonelli et al conducted a study to assess the healing of tympanic membrane perforations caused following acute otitis media after using a combination of topical dexamethasone and ciprofloxacin. They showed delayed tympanic membrane repair in a 4-week follow-up

TABLE 2 Preoperative and postoperative SRT and mean BC, AC, and ABG in frequencies of 0.5 to 3 kHz

Variables		Preoperative		Postoperative			Gain		
		Mean	SD	Mean	SD	*P*-value[a]	Mean	SD	*P*-value[b]
BC	Ciprofloxacin	12.70	6.80	8.34	5.29	<.001[c]	4.36	6.76	.047[d]
	Betamethasone	13.47	8.92	11.83	8.19	.052[c]	1.64	5.77	
AC	Ciprofloxacin	33.55	9.45	20.67	7.93	<.001[c]	12.88	6.92	.007[d]
	Betamethasone	34.68	12.73	27.73	15.18	<.001[c]	6.95	12.24	
ABG	Ciprofloxacin	21.34	8.04	12.33	4.26	<.001[c]	9.01	7.89	.160[e]
	Betamethasone	21.21	7.14	15.90	10.14	<.001[c]	5.31	10.53	
SRT	Ciprofloxacin	30.45	9.99	20.23	7.07	<.001[c]	10.23	8.62	.260[e]
	Betamethasone	32.44	15.13	25.12	12.89	.001[c]	7.33	12.60	

[a]*P*-value for within groups comparison.
[b]*P*-value for between-groups comparison.
[c]Wilcoxon.
[d]Independent samples test.
[e]Mann-Whitney test.

period after prescription of topical dexamethasone in the chinchilla model (OR: 5.5, 95% CI: 2.4-12.6).[4]

Literature review showed some studies which investigated the effect of topical quinolone on tympanic membrane healing in human. In a retrospective cohort study, the researchers mentioned that the use of ciprofloxacin plus hydrocortisone and dexamethasone ear drops was associated with increased risk of tympanic membrane perforation with an adjusted hazard ratio of 2.24 (95% CI: 1.03-4.85) and 2.30 (95% CI: 1.09-4.87), respectively.[23] Another retrospective cohort study examined the risk of perforation requiring tympanoplasty following tympanostomy tube insertion and prescribing quinolone ear drops in 96 595 children. The adjusted hazard ratios were 1.94 (95% CI: 1.32-2.85) and 2.00 (95% CI: 1.18-3.41) for ciprofloxacin plus hydrocortisone and ciprofloxacin plus dexamethasone, respectively. They concluded that using quinolone ear drops may lead to a higher risk of perforation requiring tympanoplasty.[24]

Based on our survey in the literature, prospective studies on the effect of ciprofloxacin ear drop on the graft success rate in humans are rare. There are a few prospective randomized clinical trials which have addressed the effect of quinolone and steroid on tympanic membrane repair in human. In a randomized clinical trial study, the authors showed administration of intraoperative otic suspension of ciprofloxacin was safe after 28-days in children who had undergone tympanostomy tube insertion due to middle ear effusion. The authors defined safety as the occurrence of serious or treatment-emergent adverse events detected in audiometric, otoscopic, and tympanometric evaluations. They evaluated the effect of topical ciprofloxacin on tympanic membrane healing after tympanostomy tube insertion, but not after tympanoplasty operation.[25]

The difference between our work and the above-mentioned study is that we investigated the intraoperative use of ciprofloxacin-soaked gelfoam, but the above investigations evaluated the effect of these drugs postoperatively.

There were two studies somehow similar to our research. A recent retrospective study by Eom et al evaluated the hearing outcome of tympanoplasty. The authors compared the results of type I tympanoplasty in patients over and under 65 years old. They inserted ciprofloxacin plus dexamethasone soaked gelfoam to decrease the rate of middle ear fibrosis caused by gelfoam. In the patients aged lower than 65 years, mean preoperative and postoperative AC were 35.7 and 25.2 dB, respectively. Also, the mean preoperative and postoperative BC were 16.6 and 12.2 dB, respectively. The mean ABG was reduced in the patients, but it was not statistically significant. The graft success rate in patients under 65 years of age was 93%. The results were relatively similar to our study.[8] Another retrospective research carried out by Starkweather and Friedman evaluated the graft success rate after administration of ciprofloxacin (0.3%) plus dexamethasone (0.1%) soaked gelfoam during type I tympanoplasty in 64 patients. They placed ciprofloxacin plus dexamethasone impregnated gelfoam in the middle ear and external auditory canal. They achieved a graft success rate of 95.3%. They suggested that intraoperative application of ciprofloxacin plus dexamethasone had no unfavorable effect on tympanic membrane healing.[3] Their study was different from ours in that our study is a prospective randomized clinical trial. Moreover, we applied ciprofloxacin and betamethasone soaked gelfoam in two separate groups and our results showed no significant difference in the graft success rate (100% and 97.7% in the case and control groups, respectively).

The most important advantage of our study is that it is a prospective randomized clinical trial. Hence, differences in the level of expertise can be excluded as a confounding factor. One drawback in this study was the relatively short-term follow-up period. Another limitation is the low number of participants, further study with a larger sample size must be done to confirm the results of the present study.

5 | CONCLUSION

To sum up, it seems that intraoperative ciprofloxacin had no adverse effects on the graft success rate and hearing outcome in tympanoplasty.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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