A Three Point Assessment Protocol for Tympanoplasty Outcomes: A Retrospective Analysis

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Abstract

Introduction The surgical outcome of chronic otitis media (COM) of the mucosal type in the pediatric population with high rates of recurrent tympanic membrane perforation is indeed a concern for the attending surgeon.

Objective The present study was done to evaluate the outcome of tympanoplasty in children with chronic otitis media mucosal type.

Methods A retrospective analysis of the medical records of all children, aged < 16 years old, who underwent tympanoplasty for COM of the mucosal type was performed. These patients were addressed by a three-point assessment, for predicting outcome of tympanoplasty, which included the age of the patient, addressing the nasal/pharyngeal issues, and the status of the COM (discharging or dry). Surgical success was assessed in terms of graft uptake and improvement of hearing. Factors affecting the surgical outcome were also analyzed.

Results A total of 90 children underwent type 1 tympanoplasty; 7 were lost to follow-up and 10 had incomplete audiometric results. In the 73 tympanoplasties analyzed, graft uptake was seen in 91.7% of the patients. Children with longer duration of ear discharge (> 8 years) had greater hearing loss. Children aged > 8 years old showed statistically significant higher chance of graft uptake ($p = 0.021$). Five of the six children who had graft rejection had bilateral disease.

Conclusion A three-point assessment in the management of pediatric COM of the mucosal type offers good outcomes with post-tympanoplasty graft uptake rates > 90%.

Keywords

- ▶ chronic otitis media
- ▶ mucosal type
- ▶ pediatric
- ▶ tympanoplasty
- ▶ outcomes
- ▶ assessment

Introduction

Chronic otitis media (COM) is a common condition, which occurs in children, with an incidence of 8.6% in the Indian pediatric population.¹ Persistent and recurrent otorrhea along with hearing loss are the common indications for surgical management. There is no general consensus on the age for surgery in children with COM. Higher rates of reperforation and subsequent need for revision surgery are the reasons proposed by those who oppose early surgery before the maturation of the eustachian tubes. On the other hand, recurrent ear discharge increases the risk of hearing

loss, leading to significant speech and language impairment in the formative years of the child. The proponents of early surgery opine that surgery improves the chances of hearing rehabilitation for the child.^{2–4}

Since 2012, a clinical assessment protocol was followed in our institution for the management of COM of the mucosal type in a pediatric population. The assessment had three areas of primary concern: age of the patient at presentation, assessment of the nose, the nasopharynx and the oropharynx for infective foci and presence or otherwise of a discharging ear. The present study was thus conducted with the primary objective of evaluating the short- and

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long-term outcomes of type 1 tympanoplasty among these pediatric patients, after the initiation of the assessment protocol.

Material and Methods

The present retrospective study was conducted in a tertiary care teaching hospital after obtaining approval from the Institutional Review Board (IRB No. 10505).

Participants

A review of the medical records of all children aged < 16 years old who underwent type 1 tympanoplasty for COM of the mucosal type, between January 2012 and June 2014, was performed according to the assessment protocol. Patients were excluded if they had cholesteatoma, presence of cranio-facial anomalies, undergone any other type of tympanoplasty or had < 12 months of follow-up. Data such as age, gender, status of the contralateral ear, size of the perforation, type of graft material used (temporalis fascia versus cartilage), status of the nasopharynx, status of the graft at postoperative follow-up visits, pre- and postoperative audiograms at 3 months, 6 months and 1 year after surgery, and complications, if any, following surgery, were recorded.

Preoperative Evaluation – the Three-Point Assessment Protocol

Three parameters were included in the clinical assessment protocol as they were found in pilot testing to best predict the outcome of management of these patients.

- (a) The first parameter used in the assessment protocol was the age of the child. Tympanoplasty in children > 8 years old showed results comparable with those performed in adults. This age is believed to correspond with the maturity of the Eustachian tubes.⁵ Hence, it was considered as the cutoff age in our management protocol. However, exceptions to this were made if the child had a hearing loss > 30 dB, needed closure of the ear drum for hearing aid fitting, or if there was persistent ear discharge, significantly affecting the quality of life.
- (b) The second parameter evaluated was assessment of the nose, of the nasopharynx and of the oropharynx of these children for any foci of infection. Preoperatively, all children underwent detailed history and clinical examination, including assessment of the nasopharynx either by nasal endoscopy or by X-ray of the nasopharynx in children uncooperative for endoscopy. Allergic rhinitis, chronic adenoiditis and chronic tonsillitis were managed appropriately. Endoscopic grading was done by the Adenoid/Choana/Eustachian Tube (ACE) grading.⁶ Although published in 2016, it has been in use in our institution since 2012. On X-ray of the nasopharynx, the adenoids were graded by the Fujioka method (A/N ratio).⁷ Adenoids > A2C1E0 (as per ACE grading) or with A/N ratio > 0.5 were considered significant, and these patients were planned for adenoidectomy.

- (c) The third parameter in the assessment protocol included assessing if the ear was dry or discharging. If discharging, an ear swab was taken for culture and appropriate medication started as per sensitivity in addition to regular ear suction and toileting. In those children in whom the ear discharge was persistent despite treatment with culture-appropriate antibiotics, a mastoid reservoir was suspected, and cortical mastoidectomy was performed.

Surgical Technique

All of the surgeries were performed under general anesthesia by one of the senior consultants in the pediatric ENT unit of the hospital. A postauricular approach was used in all of the patients. Tympanomeatal flap was elevated, and temporalis (TM) fascia graft or conchal cartilage with TM fascia was used. The choice of graft material was dependent on the preference of the surgeon. Type 1 tympanoplasty was performed in all of the patients. If cortical mastoidectomy was planned, it was performed prior to graft placement. Exenteration of all mastoid air cells was performed along with widening of the aditus ad antrum. A free flow of saline ensured the patency of the aditus. The graft was placed using the underlay technique, and the wound was closed in layers. Adenoidectomy was performed at the same sitting, according to the institutional protocol.⁶

Follow-Up

Graft uptake was assessed at 3 months, 6 months and 1 year following the surgery. Pure tone audiogram was performed preoperatively, and at 3, 6 and 12 months postoperatively. Hearing outcomes of the patients were measured by comparing the pre- and postoperative hearing thresholds, calculated at 0.5, 1, and 2 kHz.

Data Analysis

The data were entered, and the results were analyzed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). The Fisher exact test was used to compare the data between those with graft uptake and graft failure.

Results

A total of 90 children aged ≤ 16 years old, who underwent tympanoplasty for COM of the mucosal type ear perforation were included in the study. Of the 90 children, 7 were lost to follow-up, and the follow-up audiometric data were incomplete in 10 children. Therefore, the data were analyzed for 73 tympanoplasties.

A total of 67 of the 73 children showed a successful graft uptake at 3 months, (91.7%) which continued to remain so throughout the follow-up period of 1 year. The demographic data of the study population are shown in **Table 1**. Although we preferred ≥ 8 years old as our cutoff, 4 children below that cutoff were operated on for reasons of persistent discharge² and hearing aid fitting²

The average duration of ear discharge in the present study was 7.11 years. The mean preoperative bone threshold was 9.58 ± 2.17 dB. The mean preoperative and postoperative air thresholds at 3 months, 6 months, and 1 year were

Table 1 Demographic Data of the Children who Underwent Tympanoplasties

Number of Tympanoplasties	73
Mean Age (years old)	11.8 (6-16)
Male to female ratio	7:5
Success rate at 3 months	91.7 % (67 out of 73)
Success rate at 6 months	91.7 %
Success rate at 1 year/2 years	91.7 %

30.97 ± 2.54 dB, 20.4 ± 2.19 dB, 22.6 ± 3.42 dB, and 20.4 ± 2.19 dB, respectively. The average preoperative air-bone gap was 21.39 dB, while the postoperative air-bone gap was 10.97 dB at 1 year of follow-up. The pre- and postoperative audiometric results are shown in ►Table 2. There was an average reduction of air-bone gap by 10.42 dB in our study. Children with longer duration of ear discharge were found to have greater hearing loss. (►Fig. 1).

The ear culture of discharging ears revealed *Pseudomonas* in nine ears, Methicillin sensitive *Staphylococcus aureus* in six, and *Enterococcus* and *Streptococcus pneumoniae* in one ear. No complications were recorded in this study group.

A total of 6 of the 73 tympanoplasties failed. All of the failures in our series were early failures. None of the children with graft uptake confirmed in the 3-month visit had late failures or perforations. ►Table 3 compares the role of various factors in those with graft uptake and those with graft failure. ►Fig. 2 shows the graft uptake percentage across increasing age groups; as can be inferred, the graft uptake is higher in older age groups. The lowest percentage was in the age group of ≤ 8 years old; children aged ≥ 8 years old showed a higher chance of graft uptake as compared with those < 8 years old ($p = 0.021$). Since the sample size was small and the data is retrospective, its statistical significance is doubtful. However, the trend that tympanoplasty has better results in older age groups cannot be ignored.

Discussion

The timing of tympanoplasty for pediatric COM of the mucosal type of has been controversial.^{3,4} Numerous publications have assessed factors influencing the outcome of pediatric tympanoplasty.^{2,4,8-10} There are conflicting reports from different parts of the world with varying

Table 2 Pre- and Postoperative Audiometric Results

	AC thresholds	BC thresholds	AB gap
Preoperative	30.97 ± 2.54 dB	9.58 ± 2.17 dB	21.39 dB
Postoperative 3 months	22.4 ± 2.08 dB	10.20 ± 3.48 dB	12.20 dB
Postoperative 6 months	22.6 ± 3.42 dB	9.43 ± 2.04 dB	13.17 dB
Postoperative 1 year	20.4 ± 2.19 dB	9.43 ± 2.35 dB	10.97 dB

Abbreviations: AC, Air Conduction; BC, Bone Conduction; AB, Airbone.

Fig. 1 Degree of hearing loss in relation to duration of ear discharge. This figure shows that average hearing loss increased as the duration of ear discharge increased.

population subgroups, on the role of age, the status of the contralateral ear, the role of adenoids and the type of graft material.^{2-4,8-11} Our success rate of 91.7% was comparable to the successful outcome of adult tympanoplasty.

Traditionally, tympanoplasty in children has been preferred at an older age; however, recent reports have challenged these notions.¹¹ Friedman et al have reported a 93% graft uptake rate in a group of 43 children < 7 years old and did not find age to be a significant prognostic determinant.¹² Other authors have also opined that age is not a significant prognostic factor.^{8,11,13} In our series, we noted that children who were operated above the age of eight years old had better outcomes after surgery. The proponents of tympanoplasty at a later age have cited recurrent otitis media in younger children and poor Eustachian tube maturity as the reasons for lower success rate in younger children.³ As we did not have a representative sample size in the age group < eight years old, no statistical significance is inferred, but this trend justifies the inclusion of age in our three point assessment protocol. All of the failures in our series were early failures. None of the children with graft uptake confirmed in the 3-month visit had late failures or perforations.

Our study also noted that hearing loss increased with an increase in the duration of otitis media (OM). This can compromise subsequent postoperative hearing results. This also justifies early surgery in children, so as to prevent further hearing loss and its subsequent sequelae. Besides, chronic pathological changes in the middle ear can lead to poor aeration and fibrotic adhesions and poor ossicular movement increasing the Airbone gap (ABG).¹⁴

The outcomes of tympanoplasty in a discharging ear have been studied by many authors, where most believe that the presence or absence of otorrhea at the time of surgery does not affect the graft uptake.^{4,15} In contrast, Onal et al in 2005 have concluded that a longer period of dry ear has a positive influence on the success of tympanoplasty.⁹ In the case of continuing ear discharge in spite of giving appropriate antibiotics (according to pus culture), concurrent cortical

Table 3 Role of Various Factors in Outcomes of Pediatric Tympanoplasty

Possible predictors	Predictors	Graft uptake (n = 67) N (%)	Graft failure (n = 6) N (%)	p-value
Size of perforation	< 50%	10 (15)	2 (33.3)	0.25
	≥ 50%	57 (85)	4 (66.6)	
Type of graft	TM fascia	54 (80)	4 (66.6)	1.000
	Conchal cartilage with TM fascia	13 (19.4)	2 (33.3)	
Status of contralateral ear	Normal	36 (54)	1 (17)	0.11
	Otitis media	31 (46)	5 (73)	

Abbreviation: TM, Tympanic membrane.

mastoidectomy with tympanoplasty was performed in our series. The role of mastoidectomy with tympanoplasty for an ear with perforation has been under debate for a long time. Albu et al, in their prospective, randomized study on 320 patients, did not find any additional benefit of mastoidectomy with tympanoplasty as far as graft uptake was concerned.¹⁶ Similar inferences have been gathered by Mishiro et al and by Toros et al in their retrospective studies.^{17,18} McGrew et al reported that mastoidectomy improved the underlying disease condition and reduced the need for further surgery.¹⁹ Cortical mastoidectomy was performed in all patients with persistent ear discharge in our study, hence the exact benefit of cortical mastoidectomy cannot be definitely concluded from the present study.

The nose and the nasopharynx were assessed in all patients, either by nasal endoscopy or by X- ray of the nasopharynx, in case of children who were not cooperative for nasal endoscopy. Recent studies have implicated bacterial colonization of the adenoids with middle ear pathogens to be

the factor responsible for OM, rather than mechanical obstruction by the adenoids per se. In children from certain populations with high prevalence of OM, it was shown that increased amounts of pathogenic bacteria in the nasopharynx increased the risk of OM.²⁰ Charlett et al, in their retrospective study, did not find any benefit of adenoidectomy prior to myringoplasty, while Gianoli et al reported more long-term successful outcomes in those who had prior adenoidectomy.^{21,22} Our patients underwent concurrent adenoidectomy/tonsillectomy if indicated.

There was no significant difference in the graft uptake rate between the two graft materials used, size of perforation, and those who had normal or diseased contralateral ear (→ **Table 2**). The status of the contralateral ear has been studied as a prognosticating factor predicting tympanoplasty outcomes, with mixed opinions. Uyar et al and Collins et al have reported a lower success rate in those with contralateral disease, while Singh et al have found no significant association between the two.^{11,23,24} In our study, five of the six children who had graft

Fig. 2 Pediatric tympanoplasty graft uptake percentage across increasing age groups.

failure had bilateral disease and had graft failure by the 3rd postoperative month. Although our study does not show the status of the contralateral ear to influence graft failure, the fact that all children with graft failure had bilateral disease cannot be ignored. Larger prospective studies would be needed to study this association.

The two predominant graft materials used in our study were temporalis fascia, and temporalis fascia supported by conchal cartilage. There was no significant difference in the graft uptake between these two groups. Given the retrospective nature of our study, there could have been several sources of bias, such as the two groups having different sample size, and the choice of graft material largely depending on the preference of the surgeon. There has been no consensus so far about the ideal graft material for tympanoplasty. Kaya et al and Çayir et al have reported a high success rate (96–97%) with cartilage tympanoplasty; similar results have been noted by Ozbek, Yegin and Friedman et al.^{10,12,25–27} On the other hand, Demirci, Şen et al and Özdamar et al have noted no difference in cartilage and fascia tympanoplasties; whereas Bozdemir et al found better results with fascia, compared with conchal cartilage.^{28–31} Mohamad et al, in their systematic review, reported that tympanoplasties with cartilage to have a better morphological outcome than fascia; however, they did not find much difference in hearing outcomes.³²

In our study, most children had near normal hearing to begin with, which improved or remained static after tympanoplasty. A meta-analysis and systematic review conducted by Hardman et al reports that only 88.8% of the cases achieve a post-operative ABG of < 30 dB. ensuring adequate TM mobility, good TM-ossicular linkage, and good aeration are factors which can affect hearing outcomes and depend a lot on surgical technique and graft material.⁸

The major limitation of the present study was that it was a retrospective analysis and has all the biases associated with it. However, it gives preliminary data on the feasibility of this protocol to improve tympanoplasty outcomes. Our three point assessment protocol is user-friendly and practical in evaluating a child planned for tympanoplasty. This can form the basis for a prospective study to evaluate surgical outcomes.

Conclusion

In the management of pediatric chronic otitis media of the mucosal type, considering the age of the child, assessing the nasopharynx/oropharynx and stage of the mucosal disease are the key principles of our assessment protocol, which increased the success rate of long-term graft uptake to > 91% of our patients. Our clinical assessment protocol for planning management of children with COM of the mucosal type is simple, easy to use, and can be followed by ENT fraternity to improve the success of graft uptake.

Children who are > 8 years old appear to have better outcomes after tympanoplasty. However, longer duration of ear discharge is associated with increased level of hearing loss, suggesting the need for earlier intervention for the

control of discharging ears in these patients. Both of these factors have to be balanced to achieve optimal surgical results. Hearing gains tend to show less variation in a 1-year follow-up. Five of the six failures due to graft rejection in our study were in younger children with bilateral large perforations. Besides, all of those who had graft failures were early failures within 3 months. Once the graft takes up, it is likely to stay so in our experience. Prospective studies with larger sample size in the Indian population can help us further elucidate the role of these factors.

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Conflict of Interests

The authors have no conflict of interests to declare.

References

- Sophia A, Isaac R, Rebekah G, Brahmadathan K, Rupa V. Risk factors for otitis media among preschool, rural Indian children. *Int J Pediatr Otorhinolaryngol* 2010;74(06):677–683
- Knapik M, Saliba I. Pediatric myringoplasty: a study of factors affecting outcome. *Int J Pediatr Otorhinolaryngol* 2011;75(06):818–823
- Sarkar S, Roychoudhury A, Roychoudhuri BK. Tympanoplasty in children. *Eur Arch Otorhinolaryngol* 2009;266(05):627–633
- Skolnick JS, Mantle B, Li J, Chi DH. Pediatric myringoplasty: factors that affect success—a retrospective study. *Laryngoscope* 2008;118(04):723–729
- Umapathy N, Dekker PJ. Myringoplasty: is it worth performing in children? *Arch Otolaryngol Head Neck Surg* 2003;129(10):1053–1055
- Varghese AM, Naina P, Cheng AT, Asif SK, Kurien M. ACE grading—A proposed endoscopic grading system for adenoids and its clinical correlation. *Int J Pediatr Otorhinolaryngol* 2016;83:155–159
- Fujioka M, Young LW, Girdany BR. Radiographic evaluation of adenoidal size in children: adenoidal-nasopharyngeal ratio. *AJR Am J Roentgenol* 1979;133(03):401–404
- Hardman J, Muzaffar J, Nankivell P, Coulson C. Tympanoplasty for Chronic Tympanic Membrane Perforation in Children: Systematic Review and Meta-analysis. *Otol Neurotol* 2015;36(05):796–804
- Onal K, Uguz MZ, Kazikdas KC, Gursoy ST, Gokce H. A multivariate analysis of otological, surgical and patient-related factors in determining success in myringoplasty. *Clin Otolaryngol* 2005;30(02):115–120
- Kaya I, Benzer M, Gode S, Sahin F, Bilgen C, Kirazli T. Pediatric type 1 cartilage tympanoplasty outcomes: A comparison of short and long term hearing results. *Auris Nasus Larynx* 2018;45(04):722–727
- Singh GB, Arora R, Garg S, Kumar S, Kumar D. Paediatric tympanoplasty: comparative study between patients aged 5–8 years and those aged over 14 years. *J Laryngol Otol* 2016;130(07):635–639
- Friedman AB, Gluth MB, Moore PC, Dornhoffer JL. Outcomes of cartilage tympanoplasty in the pediatric population. *Otolaryngol Head Neck Surg* 2013;148(02):297–301
- Singh GB, Sidhu TS, Sharma A, Singh N. Tympanoplasty type I in children—an evaluative study. *Int J Pediatr Otorhinolaryngol* 2005;69(08):1071–1076
- Kent DT, Kitsko DJ, Wine T, Chi DH. Frequency-specific hearing outcomes in pediatric type I tympanoplasty. *JAMA Otolaryngol Head Neck Surg* 2014;140(02):106–111

- 15 Albera R, Ferrero V, Lacilla M, Canale A. Tympanic reperforation in myringoplasty: evaluation of prognostic factors. *Ann Otol Rhinol Laryngol* 2006;115(12):875–879
- 16 Albu S, Trabalzini F, Amadori M. Usefulness of cortical mastoidectomy in myringoplasty. *Otol Neurotol* 2012;33(04):604–609
- 17 Mishiro Y, Sakagami M, Kondoh K, Kitahara T, Kakutani C. Long-term outcomes after tympanoplasty with and without mastoidectomy for perforated chronic otitis media. *Eur Arch Otorhinolaryngol* 2009;266(06):819–822
- 18 Toros SZ, Habesoglu TE, Habesoglu M, et al. Do patients with sclerotic mastoids require aeration to improve success of tympanoplasty? *Acta Otolaryngol* 2010;130(08):909–912
- 19 McGrew BM, Jackson CG, Glasscock ME III. Impact of mastoidectomy on simple tympanic membrane perforation repair. *Laryngoscope* 2004;114(03):506–511
- 20 Smith-Vaughan H, Byun R, Nadkarni M, et al. Measuring nasal bacterial load and its association with otitis media. *BMC Ear Nose Throat Disord* 2006;6:10
- 21 Charlett SD, Knight LC. Pediatric myringoplasty: does previous adenoidectomy improve the likelihood of perforation closure? *Otol Neurotol* 2009;30(07):939–942
- 22 Gianoli GJ, Worley NK, Guarisco JL. Pediatric tympanoplasty: the role of adenoidectomy. *Otolaryngology-head and neck surgery*. 1995;113(04):380–386
- 23 Uyar Y, Keleş B, Koç S, Öztürk K, Arbağ H. Tympanoplasty in pediatric patients. *Int J Pediatr Otorhinolaryngol* 2006;70(10):1805–1809
- 24 Collins WO, Telischi FF, Balkany TJ, Buchman CA. Pediatric tympanoplasty: effect of contralateral ear status on outcomes. *Arch Otolaryngol Head Neck Surg* 2003;129(06):646–651
- 25 Çayır S, Kayabaşı S. Type 1 tympanoplasty in pediatric patients: Comparison of fascia and perichondrium grafts. *Int J Pediatr Otorhinolaryngol* 2019;121:95–98
- 26 Ozbek C, Ciftçi O, Tuna EE, Yazkan O, Ozdem C. A comparison of cartilage palisades and fascia in type 1 tympanoplasty in children: anatomic and functional results. *Otol Neurotol* 2008;29(05):679–683
- 27 Yegin Y, Çelik M, Koç AK, Küfeciler L, Elbistanlı MS, Kayhan FT. Comparison of temporalis fascia muscle and full-thickness cartilage grafts in type 1 pediatric tympanoplasties. *Rev Bras Otorrinolaringol (Engl Ed)* 2016;82(06):695–701
- 28 Demirci S, Tuzuner A, Karadas H, Acıkgoz C, Caylan R, Samim EE. Comparison of temporal muscle fascia and cartilage grafts in pediatric tympanoplasties. *Am J Otolaryngol* 2014;35(06):796–799
- 29 Şen A, Özdamar K. Endoscopic tympanoplasty with limited tympanomeatal flap elevation in pediatric cases: comparison of anatomic and audiological results of grafts. *Eur Arch Otorhinolaryngol* 2019;276(09):2427–2432
- 30 Özdamar K, Sen A. Comparison of temporal muscle fascia and tragal cartilage perichondrium in endoscopic type 1 tympanoplasty with limited elevation of tympanomeatal flap. *Rev Bras Otorrinolaringol (Engl Ed)* 2019
- 31 Bozdemir K, Kutluhan A, Yalciner G, Tarlak B, Bilgen AS. Tympanoplasty with island cartilage or temporalis fascia: a comparative study. *ORL* 2012;74(01):28–32
- 32 Mohamad SH, Khan I, Hussain SS. Is cartilage tympanoplasty more effective than fascia tympanoplasty? A systematic review. *Otol Neurotol* 2012;33(05):699–705