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Letter to the Editor

Letter to the Editor Regarding "Esterified Hyaluronic Acid Placed in the Middle Ear Does Not Improve Outcomes in Cholesteatoma Surgery"

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Dear Editor,

We studied with great enthusiasm the article written by Leonard et al (2022) entitled "Esterified Hyaluronic Acid Placed in the Middle Ear Does Not Improve Outcomes in Cholesteatoma Surgery."[1] The authors carried out a non-randomized prospective cohort study on children with cholesteatoma who underwent primary surgeries to investigate the effect of hyaluronic acid (HA) sheets on cholesteatoma recurrence and middle ear pressure.[1] The authors concluded that HA sheets do not reduce the recurrence of cholesteatoma. However, the doubtful methods and results of the study are highly ambiguous.[1]

(I) In their methods, 126 children were allocated into heterogeneous groups: 63/126 patients received HA as a sheeting material (EpiFilm) but not a filling material, of which 58/63 received only HA sheets and 5/63 patients received HA sheet + Gelfoam to support the HA sheet or tympanic membrane (TM) graft material (temporalis fascia or tragal cartilage).[1] On the other hand, as their control group, 63/126 patients did not get HA sheets, and 12/63 cases only got Gelfoam. It is also surprising that the authors did not use any filling or sheeting material to support the TM graft in 51/63 ears.[1] Since an appropriate supporting material is usually applied to prevent the displacement of the TM graft, we are curious to know how the authors became assured about preventing TM graft displacement in those 51 ears (40.4%) without any supporting material (Gelfoam or HA sheet) and what happened to their postoperative status of middle ear mucosa and the rate of retraction pocket.[1] They also excluded 3 cases in which patients were given HA sheets during canal wall down (CWD) mastoidectomy. The retraction pocket is only seen in canal wall up mastoidectomy, but they did not specify how many CWD cases were in their control group.[1]

(II) Regarding the results section, the reported number of patients who received temporalis fascia as a TM graft in the first paragraph of this section is in contradiction with the numbers displayed in Table 2.[1] Furthermore, they did not explain why 28% of patients' middle ear pressure could not be measured.[1]

(III) The authors defined recurrence of cholesteatoma as the formation of cholesteatoma in the new TM retraction pocket, postoperatively.[1] We believe that there is a misconception in setting the impact of TM sheeting material on the postoperative retraction pocket as the primary hypothesis. There are some key pathogenesis factors for retraction pockets, such as eustachian tube dysfunction, recurrent acute otitis media or otitis media with effusion which is frequent in children, and degeneration of the middle collagenous fibrous layer caused by inflammation.[2] In addition, an appropriate reconstruction of the attic and scutum prevents the recurrence of the retraction pocket.[3]

(IV) Some eminent researchers in the field of otology confirmed that cartilage tympanoplasty reduces the incidence of retraction pocket.[4] Hence, the significantly higher utilization of cartilage in the non-HA group compared to the HA group (35% vs. 19%) constitutes a major confounding factor that cannot be easily disentangled from the primary conclusion of this study.

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Author's Response

We appreciate the correspondents' thoughtful interest in our manuscript[1] and the opportunity to respond to their comments.

As they point out, esterified hyaluronic acid (eHA) sheeting was not used as a packing material. It was placed as a lining material to try and prevent adhesive scar formation. Absorbable gelatin sponge (AGS) was placed to support the tympanic membrane graft in a small and similar number of cases in each group in our study (p=0.12, Fishers exact test). We have minimised the use of AGS packing in the middle ear because of concern from animal models that it promotes adhesion formation.[2,3] We instead suspend the graft from one side of the ear canal to the other. A small amount of AGS is only placed as an adjunct to optimise graft position if needed. Our published perforation closure rate matches that found in meta-analysis of paediatric tympanoplasty confirming that routine packing of the middle ear is not required for effective tympanic membrane reconstruction.[4-7]

On the basis that AGS packing is assumed to provide only temporary support to the TM repair, we would not expect its use to prevent post-operative retraction. Data on post-operative TM retraction were not recorded during the study period. Instead, tympanometric measurement of middle ear pressure (MEP) and recurrent cholesteatoma rate were used as outcome measures. Tympanometry was always completed except in rare cases when children objected. TM compliance was not sufficient to measure MEP in 28% of cases, such as happens in the presence of a middle ear effusion, TM perforation or sometimes with a large cartilage graft.

Cases of canal wall down tympanomastoidectomy cases were excluded from this study because of the expected differences in middle ear pressure regulation and recurrence after exenteration of the mastoid: there were none in the eHA or control group.

We are grateful to the correspondents for pointing out the discrepancy in reporting number of ears repaired with temporalis fascia for which we apologise. We have reviewed the data set and found that the numbers reported in Table 2 are correct (51 of eHA group with fascia and 35 of the control group).

The principle underlying this study, as outlined in the introduction of the manuscript, is that impaired tympanomastoid ventilation is one factor that contributes to negative pressure and recurrent cholesteatoma from tympanic membrane retraction. We hypothesized that eHA might improve ventilation by preventing obstructive scar formation. That other factors may also contribute to recurrence of cholesteatoma, particularly Eustachian tube dysfunction, does not negate the validity of this question. As type and stage of cholesteatoma (Tables 1 and 2) were similar in each group, we assume that other patient related factors might be similarly distributed in the eHA and control groups, though of course randomization of allocation to intervention would be required to minimise this risk of bias. Nevertheless, the OCEBM level 3 evidence provided by our study is potentially more reliable than the level 5 evidence cited by the correspondents.

Surgeons' techniques often evolve with time and experience. To try and minimise this effect on outcome, we selected our control group from cases completed before and after the time period in which eHA was used. Despite this study design, cartilage was used more often for reconstruction in the control group which might be expected to reduce the risk of recurrence in comparison with the eHA group (though not negative middle ear pressure). Although not clearly reported in the manuscript, the data on cartilage use were only described for tympanic membrane reconstruction. When including cases in which cartilage was used for scutum reconstruction, the difference in its use between groups is not significant (cartilage used for 25 ears in eHA group and 30 ears in control group (p=0.4 Chi square test)). It is also of note that a soft tissue graft was only used once in each group for scutum reconstruction. Multifactorial analysis of our data shows that the use of neither eHA (HR 0.63 95% CI [0.20, 1.96], cartilage (HR 1.60 95% CI [0.53, 4.83] nor AGS (HR 1.10 95% CI [0.24, 5.14] had any significant effect on the risk of recurrent cholesteatoma (p>0.4, Cox regression analysis). So although unequal use of cartilage between groups is a limitation of our study, we doubt that it significantly altered the outcomes.

We appreciate the opportunity to clarify aspects of our data and manuscript in response to the correspondents' comments but stand by our conclusion that we were unable to detect a clinically meaningful benefit from use of eHA in cholesteatoma surgery.

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