

Peer Review File

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Reviewer A

I congratulate the authors on an excellent systematic review which has followed all the required international and validated guidelines as well as statistical analysis. This is a critical review which adds evidence-based knowledge to the challenging clinical management of labyrinthine fistulae repair.

Reviewer B

This is a systematic review comparing endoscopic under-irrigation solution (UWEES) to traditional microscopic repair of labyrinthine fistula secondary to cholesteatoma.

The study is excellently presented, systematic in its approach and provides an insightful discussion. The majority of the methods, introductions, and discussion are appropriate and informative.

However, the paper should not assert conclusions unsupported by the results, or literature, in the authors' enthusiasm for this novel technique. The discussion can be misleading when discussing totally endoscopic cholesteatoma removal techniques. This should not be confused with UWEES, which is mostly performed in combination with an open mastoidectomy. The meta-regression analysis is also at risk of overfitting (due to <5 studies per covariate/moderator included) and ecological fallacy (by drawing conclusions on effect size from aggregate level characteristics e.g. mean age, % female). These risks, or if any strategies were performed to mitigate these risks should also be included.

Comment 1: asserting conclusions unsupported by results including discussion re endoscopic techniques.

Reply 1: Thank you very much for the critical feedback. We have made the following edits to the manuscript to clarify the UWEES technique as well as a rewritten discussion to better address UWEES and microscopic techniques alone.

Changes in the text:

1. Introduction line 119: 'An open mastoidectomy is first performed, and the matrix removal is left as the last operative step, as in traditional microscopic techniques.'
2. Discussion line 314-330: 'This systematic review shows that UWEES may be a safe and effective alternative to the microscopic approach. Efficacy was measured as stable or improved hearing outcome and low rate of secondary complications. The results showed there was no statistically significant difference in both mean bone conduction thresholds pre- and post-operatively as well as proportion of improved bone conduction threshold post-operatively for both UWEES and microscopic methods. Both techniques begin with a canal-wall up or canal-wall down mastoidectomy, with the UWEES technique then involving a fistula repair under continuous irrigation, while the microscopic approach performs the fistula repair with the cavity exposed to air. The microscopic approach carries a risk of suctioning of the perilymph and

accidental damage of the membranous labyrinth which may result in irreversible hearing loss. To reduce this risk, a staged procedure is often used, with the complete fistula matrix removed at the second look operation. In other cases, a thin layer of matrix is left intact over the fistula, however this leaves a potential source for ongoing bony erosion and delayed sensorineural hearing loss. UWEES addresses these complications by creating a fluid filled chamber that mimics perilymph, thereby decreasing direct suctioning of the delicate membranous labyrinth and preventing pneumolabyrinth.

3. Discussion line 338-349: ‘This work found that while the UWEES method had no significant association with risk reduction of vertigo post-operatively, the microscopic approach was associated with a statistically significant risk reduction of vertigo post-operatively. However, significant heterogeneity was observed in this outcome. Additional factors that have been considered to influence vertigo outcomes include the choice of repair material. There are suggestions that the ‘sandwich technique, involving a layer of temporal fascia, followed by bone pate, and another layer of temporal fascia, is associated with a lower occurrence of post-operative vertigo. It has also been proposed that mastoid obliteration could serve as a barrier for external ear canal induced pressure changes, which have been implicated in the onset of vestibular symptoms following removal of the fistula matrix.’
 4. Discussion line 370-380: ‘The rate of recidivism post operatively for the UWEES group was also comparable with microscopic in this systematic review, and both had very low rates of facial nerve weakness secondary to repair. However, the follow up period was relatively short in both groups, with an average length of follow up of 42 months in the UWEES and 29 months in the microscopic group. The existing literature suggests that recurrence rate is significantly higher in patients with more than 10 years of follow up. Canal-wall down mastoidectomy has also been associated with a lower rate of both residual and recurrent disease, presumably due to the more extensive visualisation from removal of the posterior canal wall. The advantage of the UWEES technique is that the endoscope provides a wide viewing angle, allowing better visualisation of the typically obscured recesses of the middle ear cavity, which may be useful in detecting residual disease.’
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Comment 2: risk of overfitting with meta-regression analysis

Reply 2: we have included a statement in regards to this risk.

Changes in the text: Discussion line 402: ‘The meta-regression analysis faces potential risks of overfitting given its small sample size of 4 studies per moderator, as well as ecological fallacy from drawing conclusions on effect size from aggregate level characteristics. Therefore, findings from this meta-regression analysis should be interpreted with caution, particularly when considering its applicability to larger populations.’

Some other minor points to address are listed below:

- Line 74 (and Table 2): consider including locations (and frequency) of other labyrinthine fistulae.

Reply 3: due to the low incidence of other fistulae locations, they were analysed as lateral semicircular canal fistulae vs others (superior and posterior). We have added this

explanation in the text

Changes in the text: Results line 304-309: ‘Factors such as lateral semi-circular canal fistula (vs superior/posterior canal fistula), primary surgery (vs revision surgery) and positive fistula sign (vs negative fistula sign) were associated with increase in the difference in risk of vertigo’

- Line 83: “the novelty of the study” should read “the novelty of the technique”

Reply 4: this has been amended

Changes in the text: abstract line 93: ‘Limitations including a lack of raw data overall and inadequate follow up time in some patients due to the novelty of the technique.’

- Line 122: “as well as pre-existing cognitive biases from surgeons trained using traditional microscopic approaches”. This statement should be removed as it is not scientific. Unlike other aspects of endoscopic ear surgery (e.g. decreased post operative pain, residual cholesteatoma) there is no current evidence demonstrating better outcomes with UWEES over traditional open fistula techniques – hence the submitted study. Limited use of a novel technique without proved benefit does not suggest a “cognitive bias”.

Reply 5: we have removed this sentence from the text

Changes in the text: introduction line 128: ‘Whilst positive results have been shown, this technique is not yet widely used due to factors such as the technical novelty and the associated learning curve.’

- Line 166: “Where studies group BC unchanged and worsened in one group, it was also taken as all BC unchanged.” Why were patient groups with mixed (unchanged/worsened) bone conduction outcomes included as unchanged? Could this be addressed by the authors given it is the primary outcome?

Reply 6: apologies, this was written in error. There were no studies which had a patient group with both unchanged or worsened hearing outcomes. One study only explicitly stated the patients whom had either worsened or improved hearing outcome. The rest of the patients in that study were taken to have unchanged hearing outcome. A review of all the included studies has been completed to confirm this. The manuscript has been changed to reflect this.

Changes in the text: Methods line 178-179: “In studies where only patients with worsened or improved hearing outcomes were explicitly described, the remainder of patients were taken to have unchanged hearing outcomes.”

- Line 224: “and available” should read “and are available”

Reply 7: we have made this change

Changes in the text: results line 237: ‘and are available as a supplement’

· Line 311-321: The paragraph discussing vertigo should be revised. It should acknowledge the study results demonstrating a reduction in vertigo in the microscopic, but not UWEES approaches but with significant heterogeneity. The remainder of the paragraph is irrelevant to UWEES (which requires an open mastoidectomy). The authors could consider including sources citing differences between endoscopic and microscopic cholesteatoma approaches in the literature.

Reply 8: This paragraph has been revised, including removal of the irrelevant discussion, and focusing on additional factors influencing the occurrence of post-operative vertigo. A statement addressing the heterogeneity has been added.

Changes in the text: Discussion line 338-349: ‘This work found that while the UWEES method had no significant association with risk reduction of vertigo post-operatively, the microscopic approach was associated with a statistically significant risk reduction of vertigo post-operatively. However, significant heterogeneity was observed in this outcome. Additional factors that have been considered to influence vertigo outcomes include the choice of repair material. There are suggestions that the ‘sandwich technique, involving a layer of temporal fascia, followed by bone pate, and another layer of temporal fascia, is associated with a lower occurrence of post-operative vertigo. It has also been proposed that mastoid obliteration could serve as a barrier for external ear canal induced pressure changes, which have been implicated in the onset of vestibular symptoms following removal of the fistula matrix.’

· Line 383-387: “The benefit of UWEES...” this paragraph should be revised as the conclusions stated do not match the data in the study (the abstract conclusion in Lines 79-84 is more appropriate). There has been no demonstrated superior benefit of UWEES over microscopic technique. There is also a reduction in post operative vertigo outcomes in the microscopic group not demonstrated with UWEES (though with high heterogeneity).

Reply 9: The conclusion has been adjusted to more accurately reflect the study outcomes.

Changes in the text: Conclusion line 430-438: ‘UWEES is a novel technique which has been used with at least short-term success in the repair of labyrinthine fistulae secondary to cholesteatomas. This systematic review supports the existing literature with comparable hearing outcome and rate of recidivism between UWEES and microscopic methods. There was a reduction in post operative vertigo in the microscopic group not demonstrated in the UWEES, however with high heterogeneity. Further research comparing both UWEES and microscopic methods in a single study with extended follow up is required.’
