Peer Review File

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Reviewer A

An outstanding retrospective review of 11 patients who underwent UWEES for high-grade labyrinthine fistulae repair. The authors have included all detailed data and information concerning preoperative, intraoperative findings and postoperative outcomes that can genuinely assist other surgeons in this specialised and complex field.

Can the authors please explain the use of the "tragal pump" for one patient? It is not clear whether this refers to a mechanism of ear drop delivery or vertigo management.

Comment 1: tragal pump
Reply 1: tragal pump for the patient in this study refers to a test for vertigo. Manual pressure is applied to the tragus causing the ear canal to close. If a labyrinthine fistula is present, this will cause increased pressure in the middle ear and then subsequently in the labyrinth. The patient will experience exacerbation of their vertigo.
Changes in the text: clarification has been added in results page 10 line 63:
'One patient had persistent vertigo beyond 6 months on tragal pressure only.'
Page 12 line 98-99:
'There was no significant vertigo post UWEES. Of the 11 patients, only 1 patient had ongoing vertigo after 6 months when examined with tragal pressure.''

Reviewer B

Editor Note: For line numbers, please see the attached "AJO-24-3-Line number" for your reference.

We thank the authors for their contribution. This study presents a cohort of about 11 patients who've underground underwater repair of perilymph fistulas. The primary outcome of the study was to demonstrate no significant different bone conduction thresholds

Major concerns:

1. Could the authors elaborate on whether the CWU or CWD surgery had an influence on the outcomes of the study?

Comment 1: CWU vs CWD
Reply 1: The main debate between CWU and CWD techniques is the control of recidivistic disease. CWD has previously been associated with a lower rate of recidivistic disease likely due to the extensive visualization from removal of the posterior canal wall. However, the consensus is that other factors such as the status of the middle ear mucosa and extent of cholesteatoma, and pre-operative hearing levels are more important in influencing outcomes. Furthermore, an advantage of the UWEES technique is that the endoscope provides a wide viewing angle, which allows visualization of the typically obscured recesses of the middle ear cavity, therefore reducing the risk of residual disease. As the focus of the study was on the safety of the UWEES technique, we did not feel it was necessary to discuss CWU vs CWD. Furthermore, the study is too small to draw accurate conclusions on whether the choice of CWU vs CWD influenced outcomes.

Changes in the text: given CWU/CWD is not the focus of this study, we have opted not to confuse the readers by discussing this at length in the manuscript. However, we have edited discussion page 13 line 105-114 to elaborate more on this:

'There was one patient with recurrent disease post UWEES (9%). This is a similar rate to both

recent UWEES studies and traditional microscopic methods which report a recurrence rate of between 10%-40% (22, 33-35). One patient in this study had residual disease (9%). Previous microscopic studies have reported residual rates of 20-30% (36-38). Most patients in this study underwent CWU mastoidectomy, which has been shown to have better protection of the exposed labyrinthine and potentially better hearing outcomes, but poorer control of recidivistic disease (39-43). Assumptions have been made that CWD is associated with lower rate of recurrent/residual disease due to the extensive visualisation with removal of the posterior canal wall (35, 44). While it is important to consider the risk of recidivistic disease, there is a consensus that the choice of surgical technique should be based preferentially on pre-operative hearing, comorbidities and extent of cholesteatoma (1, 3, 5, 16, 30). Combining UWEES technique with CWU may reduce the rates of recidivism with the wider viewing angle and clearer operative field which the UWEES approach provides, with the downside that it would increase the difficulty of revision surgery and have a higher risk of interrupting the fistula repair (45, 46). However, longer follow up times and a larger sample size are required to draw reasonable conclusions of recidivism.'

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2. Could the authors comment on the treatment of labyrinthine fistula using a CWU technique? It is common practice in microscopic surgery to treat labyrinthine fistulas with CWD techniques in order to prevent residual disease as well as to manage the fistula. The results of this paper has shown the presence of confirmed residual disease in 2 patients, and possibly in another patient. Could the authors comment on why CWU were chosen in as the primary method of disease management?

Comment 2: CWU vs CWD in control of residual disease
Reply 2: Although previous studies have shown CWD to have better control of residual disease, there have since been many more studies which conclude that surgical technique should be primarily based on factors such as pre-operative hearing levels, the extent of the cholesteatoma and comorbidities. Studies have also indicated that the combination of a CWU mastoidectomy and UWEES repair is comparable to a CWD approach, albeit with some limitations such as a more difficult revision surgery if one was required. Please refer to reply 1 and changes in text above which further elaborates. Given this, the authors felt there was no need to perform a CWD mastoidectomy if the same result could be achieved with a CWU and UWEES approach. As discussed in reply 1, the focus of the study was to assess the safety of the UWEES approach.

Changes in the text: We have added the below explanation in the Methods section page 8 line 19-20 as to the choice of CWU:

'Choice of CWU vs CWD mastoidectomy was determined on a case by case basis based on standard management algorithms including patient factors and disease factors rather than the presence of a fistula.'

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3. Could the authors define what is meant by vertigo vs unsteadiness (Page 10 line 55)?

Comment 3: vertigo vs unsteadiness
Reply 3: We considered vertigo to be the sensation of moving when one is not, most often rotational movement. Eg. Patients feeling that the world is spinning around them. We considered unsteadiness as a sensation of imbalance or postural instability i.e. swaying, rocking, feeling of almost falling.

Changes in the text: As the secondary outcome of interest is vertigo, we have removed this sentence to avoid confusion.

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4. Could the authors comment on how one patient developed a CSF leak?

Comment 4: CSF leak
Reply 4: The CSF leak was noted when dissecting cholesteatoma which was firmly adherant to the adjacent dura, having eroded the tegmen. It was repaired successfully without further leak noted.

Changes in the text: changes have been made to clarify on page 11 line 71-73:
'There were no patients with pre-operative or post-operative facial nerve weakness. One patient had an intra-operative cerebro-spinal fluid (CSF) leak noted after dissection of cholesteatoma in a region of tegmen erosion which was repaired successfully with no further leak noted. No other complications were identified.'

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5. The limitations and downsides of this new technique needs to be discussed an elaborated. Whilst hearing outcomes have not shown an change between the pre operative and post operative condition, the presence of complications (eg CSF leak), as well as a relative high rate of residual disease needs to be mentioned.

Comment 5: secondary outcomes – complications and residual disease
Reply 5: due to the low numbers in this study, it is not possible to draw accurate conclusions on rate of complications and rate of residual disease. CSF leak was secondary to cholesteatoma erosion of the tegmen and occurred during standard microscopic dissection, so is not related to the assessment of the underwater repair of the fistula. Discussion page 12 line 89 and 95 mentions previously reported rates of recurrent and residual disease for microscopic technique to be 10-40% and 20-30% respectively, which would be higher than both the rate of residual disease (9%) and rate of recurrent disease (9%) in this study. However again given the low numbers in this study, we cannot accurately say that UWEES has an advantage in this area. It is important to note, that the mastoidectomy is performed in a standard microscopic fashion, but then the endoscope is brought in as an adjunct for the fistula repair.

Changes in the text: page 12 line 105-114:

'There was one patient with recurrent disease post UWEES (9%). This is a similar rate to both recent UWEES studies and traditional microscopic methods which report a recurrence rate of between 10%-40% (22, 33-35). One patient in this study had residual disease (9%). Previous microscopic studies have reported residual rates of 20-30% (36-38). Most patients in this study underwent CWU mastoidectomy, which has been shown to have better protection of the exposed labyrinthine and potentially better hearing outcomes, but poorer control of recidivistic disease (39-43). Assumptions have been made that CWD is associated with lower rate of recurrent/residual disease due to the extensive visualisation with removal of the posterior canal wall (35, 44). While it is important to consider the risk of recidivistic disease, there is a consensus that the choice of surgical technique should be based preferentially on pre-operative hearing, comorbidities and extent of cholesteatoma (1, 3, 5, 16, 30). Combining UWEES technique with CWU may reduce the rates of recidivism with the wider viewing angle and clearer operative field which the UWEES approach provides, with the downside that it would increase the difficulty of revision surgery and have a higher risk of interrupting the fistula repair (45, 46). However, longer follow up times and a larger sample size are required to draw reasonable conclusions of recidivism.'

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6. It is not clear that there is an advantage over the microscopic technique from this manuscript. Could the authors elaborate on what the advantages are based on their series? This would help the reader understand the justification for using using this technique. For example, is this technique less time consuming?

Comment 6: advantages of UWEES technique

Reply 6: Potential advantages of UWEES include better visualization of the repair with a wider viewing angle provided by the endoscope, less damage from direct suctioning of the membranous labyrinthine as well as less damage to the membranous tissue from exposure to air.

Changes in the text: we have elaborated on the potential advantages further in the introduction page 6 lines 91-98 and discussion page 11 line 75-77 and page 13 line 105-107:
Page 6 lines 91-98:

'The UWEES technique was first published in 2014 for repair of lateral semicircular fistula technique and this technique may overcome several issues associated with the open microscopic dry approach (18). The microscopic dry approach requires simultaneous delicate removal of the matrix and repair. The matrix is removed with gentle suction on a neuro patty and then quickly placing the repair, minimizing exposure time of the membranous labyrinthine to air. With the underwater technique, the matrix is left intact until the last step, where the mastoid cavity is filled with body temperature isotonic water to mimic perilymphatic fluid. This minimises exposure of the delicate membranous labyrinthine tissues to air and potentially reduces electrolyte changes in the perilymph and endolymph. An endoscope with body temperature irrigation is submerged thus providing a clear operative field without requiring suction which may reduce the risk of direct mechanical damage to the inner ear (19). Another potential advantage of the UWEES technique is that the endoscope provides a wide viewing angle, allowing better visualisation of the middle ear cavity to assist in both the repair and in detection of residual disease.'

Page 11 line 79-83:
'UWEES is a relatively new technique used to treat labyrinthine fistulas secondary to cholesteatomas, with potential advantages including a wider surgical viewing angle to allow better visualisation of the middle ear cavity. The mastoid cavity is flooded with body temperature isotonic water which mimics perilymphatic fluid, potentially reducing electrolyte changes in the periplymph and endolymph, as well as damage to the membranous labyrinthine from exposure to air and direct mechanical suctioning. Underwater dissection of tissue also aids in separation of the disease from normal tissue.'
Page 13 line 111-112:
'Combining UWEES technique with CWU may reduce the rates of recidivism with the wider viewing angle and clearer operative field which the UWEES approach provides,'

Minor comments:
1. Page 9 , line 37 - it is mentioned that 1 patient had CWD but in the tables and subsequent lines 43-44, it is mentioned that two patients had a MRM. Please clarify and use consistent terminology (eg. MRM / CWD)

Comment 7
Reply 7: Apologies for the error during writing, two patients had a previous CWD.

Changes in the text: text has been edited on page 9 line 43-52:
'Patient demographics and disease characteristics are depicted in Table 2. Eleven patients (6 male, 5 female) were identified. In 8 patients CWU technique was performed to clear the ear from cholesteatoma and treat the fistula. In 3 patients the labyrinthine fistula was treated during

revision surgery (CWU in 1 case and revision CWD in 2 cases). The median age at the time of surgery was 56.4 years (range 20-80 years). No patients had an intact labyrinthine endosteum. Ten out of the eleven patients had a type II fistula (5 type IIa, 5 type IIb) and one type III. In every case temporalis fascia was used to repair the fistula. In 5 patients a 'sandwich' composed of temporalis fascia, bone pate and fascia were used, in 4 cases temporalis fascia and composite cartilage, and in 2 cases a combination of temporalis fascia, composite cartilage which was covered with bone pate after drainage. Intra-operatively, 9 patients were found to have intercurrent ossicular erosion. All 9 had incus and malleus erosion, and 2 also had stapes erosion. Five patients had fallopian canal erosion, and two patients had tegmen dehiscence. Six patients had post-operative imaging (at a mean of 21 months post-operatively). Three patients had a second look procedure in place of post-operative imaging, one patient had clinical observation only due to the previous CWD mastoidectomy, and one patient was lost to follow up.'

2. Page 8, line 26 - are the dB hearing levels in dB HL and if so, at which frequency or frequencies?

Comment 8
Reply 8: yes dB HL. Frequencies are described in line page 8 line 32.

Changes in the text: see text page 8 line 31-32.
'The primary outcome of this study is the postoperative bone conduction threshold measured in dB HL from the most recent follow-up. An audiogram tested bone conduction thresholds at frequencies of 0.5, 1, 2, and 4 kHz.'

3. Page 9, line 50 - is this difference significant?

Comment 9
Reply 9: there is no significant difference, please see page 10 line 55. There was also no significant difference in Dornhoffer type 2a and 2b hearing outcome.

Changes in the text: see page 10 line 55-59:
'A Wilcoxon signed-rank test showed that there was no significant decline of hearing after UWEES (Z= -0.664, p=0.51). We found a mean pre-operative bone conduction threshold (0.5-4kHz) of 23.3 dB (SD 15.5). After a mean of 18 months follow-up (SD 16) this increased to 25.1 dB post-operatively (SD 16.6).
Subgroup analysis of hearing improvement showed no differences between Dornhoffer type 2a and 2b ossicular reconstruction (Δ -0.5 and Δ -2.7, p=0.90 and p=0.93 respectively). The Dornhoffer type 3 ossicular reconstruction gave the poorest hearing outcomes (Table 3).'

4. Page 11, line 75-80 - what is the purpose of this reference?

Comment 10

Reply 10: We are unsure of your question. The reference refers to the study that is discussed in this paragraph, Meng et al. Could you please elaborate?

Changes in the text: see page 11 line 89-91:
'Meng et al compared microscopic and UWEES technique in two separate groups (group 1 underwent microscopic repair and group 2 underwent UWEES repair) and found that there was a significant difference in air-bone gap between the two groups for type IIa and IIb fistulas post-operatively, but not for type I (17).'

5. Page 13, line 13 - the shortest length of follow up was 15 months for one patient - could the authors elaborate on how this compared to other patients and the overall mean follow up?

Comment 11
Reply 11: The mean follow up for audiogram and the mean total follow up time is described in the lines listed below. The individual follow up times for patients is also listed in table 2: patient demographics. However, there was a typo. The shortest follow up was 13 months. This has now been amended in both the text and tables. Thank you for pointing out this error.

Changes in the text: see page 14 line 133-134, page 5 line 71, page 8 line 28, page 10 line 66 and table 2: patient demographics.
'The shortest length of follow up was 13 months for one patient. Short follow up durations were either due to patient compliance, or recent surgery at the time of review.'
'One patient (9%) had recurrent disease and one patient (9%) had residual disease at a mean follow up time of 34 months (SD 22).'
'All patients had continuous follow up with repeat audiogram at a mean of 18 months post-operatively.'
'Patients had a mean total follow up of 34 months (SD 22).'