

REPLY TO ADRION ET AL. ON PATEL ET AL.

Patel M, Arshad Q, Seemungal BM, Harcourt JP, Golding JF, Bronstein AM

We apologise for not having noticed earlier Adrion and colleagues' comments on our study comparing the effectiveness of intratympanic Methylprednisolone to Gentamicin in refractory Ménière's disease [1], covered by the BMJ [2]. Contrary to our expectations, both drugs were equally effective in controlling vertigo (primary outcome).

Adrion's primary concerns were, (i) that negative studies pose the problem of "not knowing how to interpret the non-significant results in a clinically relevant way" and, (ii) the lack of a power calculation for the primary outcome.

Regarding (i), our interpretation is that given the known ototoxic effects of gentamicin, ascertaining any minuscule difference between the two drugs is not justified and, very likely, unethical. A further comment was that "transforming the data to achieve a more symmetric distribution may have resulted in more power when an ANOVA or t-test is applied". We agree that some of the data deviated from strict normality. There is always debate about the robustness of ANOVA in these cases, however this was addressed in the paper - non-parametric tests confirmed that there were no significant differences between Methylprednisolone and Gentamicin for vertigo outcomes (Appendix, page 6).

Adrion also recommended adjustment for baseline differences, but a crucial strength of our study was adherence to the CONSORT 2010 guidelines for transparent reporting of trials [3], which states that "Although proper random assignment prevents selection bias, it does not guarantee that the groups are equivalent at baseline. Any differences in baseline characteristics are, however, the result of chance rather than bias. The study groups should be compared at baseline for important demographic and clinical characteristics so that readers can assess how similar they were.....Adjustment for variables because they differ significantly at baseline is likely to bias the estimated treatment effect." Nevertheless, to satisfy Adrion and colleagues' concerns & for the benefit of readers, we reanalysed our primary outcome data with ANCOVA using baseline vertigo attack frequency over 6 months as covariate. As with ANOVAs and non-parametric tests, the re-analysis showed no difference between drugs ($F=.527$ d.f.=1,57 $p=.471$). In other words, performing the ANCOVA does not change our results nor add any further information for the reader.

Regarding (ii) the reason for the lack of power calculation for the primary outcome was clearly stated in our paper: "At the time of planning of our study, there were few published data on intratympanic gentamicin versus steroid treatment for Ménière's disease". Hence sample-size calculations were based on hearing outcomes where drug differences were better established [4]. However, we are now able to back-calculate our data. Depending on which outcome metric is chosen to resolve the small effects observed (vertigo attacks at 2 years, percentage reduction in vertigo attacks, absolute reduction in number of vertigo attacks, using intention to treat or per protocol), for conventional 80% power with $p=.05$ 2-tailed the numbers of patients required is between 150 to over 400 per group, thus illustrating the minute differences, if any, for the primary outcome (vertigo).

Finally, the comment "the primary endpoint may be biased since it was assessed by retrospective face-to-face interviews instead of event-oriented or daily symptom diaries", was also addressed in the paper. It would be unethical to recruit patients with refractory Meniere's disease experiencing

more than one attack per week (Table 1) and require that they fill up a diary for the next 6 months before receiving treatment. Further, all the validated vestibular questionnaires used showed no differences between Methylprednisolone and Gentamicin either. In the same vein, it would be unethical to give patients a placebo when gentamicin is clearly more effective than placebo for vertigo control (for Cochrane Review, see [5]) and it should be emphasised that a comparison between Gentamicin and Placebo led to the early termination of a randomised, double-blind, controlled trial in 2014 [6]. In view of these data, we believe that the initial treatment choice between an ototoxic drug (Gentamicin) and one that it is not (Methylprednisolone), will be simplified for most patients and doctors.

References

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- [4] Sennaroglu L, Sennaroglu G, Gursel B, Dini FM. Intratympanic dexamethasone, intratympanic gentamicin, and endolymphatic sac surgery for intractable vertigo in Meniere's disease. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* 2001; **125**(5): 537-43.
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