

Peer Review File

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Reviewer A

Comment: The authors aim to investigate whether olanzapine is effective in preventing hiccups. While this could be interesting research to prevent adverse events, the study and manuscript raise a couple of concerns.

Reply: Thank you for this short summary.

Comment. This study was enriched the patient population to include an approximately equal number of patients who did and did not receive olanzapine. Is this causing a bias between groups? In particular, metoclopramide in addition to baclofen is also effective against hiccups. It is necessary to verify whether these factors are affecting your results.

Reply: We thank this reviewer for the opportunity to respond. First, in response to this reviewer's thoughtful comment, we did re-review all the medical records and found that 20 had been prescribed baclofen around the time of cisplatin and 10 had been prescribed metoclopramide. We have modified the manuscript to now add this extra data with respect to concurrent olanzapine use and concurrent hiccup development. Please see extra paragraph under Results.

Second and more importantly, we think bias is perhaps somewhat unlikely because we did choose the patients in the enriched group in a truly random fashion (we used a computer-based randomization function to do so). We have now modified the manuscript to further explain our methods. Please see added sentence to second paragraph under Data Acquisition. Third and also more importantly, to our knowledge, no data suggest that prophylactic metoclopramide or baclofen present hiccups, so it appears less likely that these drugs served as a confounder and led to a lower incidence of hiccups in the study. We have revised the manuscript to make this point more clearly. Fourth, from a timing standpoint, it seems logical that patients who have developed hiccups would have such information reported in the medical record and would then receive either baclofen or metoclopramide. Thus, hiccups would be mentioned in the medical record, and we would be able to record them as such in our study. Again, we have modified the manuscript to make this point clearer. Please see extra paragraph under Results, as already alluded to above.

Comment: The authors need to consider more about the patient background. For cisplatin-induced hiccups, both clearance and dose of cisplatin should be considered.

Reply: Thank you. We have now reviewed all the medical records and provide information on dosing of cisplatin. Please see results. Please note that, as per standard of care clinical practice, all patients had to have had a creatinine checked prior to the administration of cisplatin, and cisplatin was administered only if the creatinine was normal. In response to this reviewer's comment, we have modified the manuscript to clarify this point. Please see extra paragraph under Data Acquisition.

Comment: In addition, although this analysis is based on the average height for gender, the examination of the distribution volume of the drugs generally uses body surface area and body weight. The authors should consider justifying why you used height and the average height value.

Reply: Please note that the data on height is based on a previous study that suggested taller people are more likely to develop hiccups. We have revised the manuscript to clarify this point. Please see extra inserted sentence under Data Acquisition.

Comment: The authors should discuss the dose of olanzapine.

Reply: Thank you. We have reviewed all the patient charts again and now provide information on olanzapine dosing. Please see the first paragraph under Results.

Reviewer B

Comment: The conclusion of the abstract states that olanzapine does not appear to palliate hiccups but given the low number of included patients with hiccups and the wide confidence intervals, I'm not sure if this conclusion is appropriate as the results may have been due to a low number of patients. Consider revising the phrasing of this statement.

Reply: Thank you. We have now revised the paper accordingly.

Comment: In the Methods section under data acquisition please consider adding if observational data was acquired retrospectively

Reply: We have modified the manuscript accordingly.

Comment: Could the results be confounded by increased used of olanzapine in patients with hiccups?

Reply: This reviewer raises an important point that confounding factors could influence the findings of all epidemiological data that report associations. Although we think it unlikely that patients would increase the use of olanzapine to treat hiccups – because of olanzapine's sedative effects – we have nonetheless modified the manuscript to address this point as a potential limitation. Please see added sentence under Discussion.

Comment: If notes medical records were reviewed for evidence of hiccups, was this routinely questioned at appointments through a standard questionnaire or was this finding dependent on clinicians asking about hiccups. It may be useful to compare the overall rate of hiccups to other studies of hiccups in cisplatin as this may indicate if hiccups were being reported accurately in your study. Please comment.

Reply: Thank you. Based on the comment above, we have now modified the manuscript to provide further information on hiccup rates with cisplatin, to provide justification for our study design, and to outline underreporting of hiccups as a limitation.

Comment. In the discussion section you mention that your observed male predominance of hiccups suggest validity of other results, could it not also mean hiccups were universally underreported?

Reply: We have now modified the manuscript to mention this issue of underreporting.

Comment: More extensive discussion of the limitations of this study is required in the discussion.

Reply: Thank you. We have now itemized limitations more clearly. Please see last paragraph in the Discussion.