

Peer Review File

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Reviewer A

Comment 1: Given the polypharmacy common in this patient population, some discussion of common drug interactions with other medications used in hospice such as morphine and especially compounding cardiac risks should be mentioned, as well as whether weight based dosing should be considered especially in this patient population.

Reply 1: We appreciate your thoughtful feedback. We have added some text to address this issue:

Added text (see Page 9-10, line 158-159):

“In this study, compounding cardiac risks were considered as exclusion criteria, but the patient was not applicable.”

Added text (see Page 13, line 228):

“, 0.26 ± 0.11 mg/kg (range: 0.11–0.61 mg/kg)”

Added text (see Page 14, line 231-232):

“A total of 17 patients (32.7 %) used opioid from chlorpromazine pre-dose; however, opioid was not adjusted or switched during the chlorpromazine treatment.”

Added text (see Page 14, line 244-245):

“No significant effect of opioid was observed on sleep quality on days 3 ($p = 0.0616$) and 7 ($p = 1.0000$).”

We have now mentioned this point in the discussion of the study limitations (see Page 20, line 342-345):

“Third, this was a prospective observational study without a control cohort. Thus, common drug interactions with other medications used in hospice, such as morphine, were not investigated. This may be believed as an acceptable limitation because sleep medications or antipsychotics were not adjusted during the chlorpromazine treatment.”

Comment 2: The authors report that the main analysis was performed "for patients who used chlorpromazine more than once..." If a significant number of patients only

took chlorpromazine once, more detail should be provided on how common this was and reasons for not continuing the intention to treat by protocol.

Reply 2: We have added this information to the Results section (see Page 14, line 241-244):

“Three patients (5.8%) only took chlorpromazine once, and reasons for not continuing were two adverse events and one death. In addition, no patients improved to a score of ≥ 4 to sleep quality on day one.”

Reviewer B

Comment 1: It is not clear whether they included patients with sleep problem as an isolated symptom, or sleep problem as part of the delirium syndrome. In this cohort of hospitalized advanced cancer patients delirium is prevalent and may reach 88% before death. Patients with delirium are likely to have sleep wake cycle disturbances, and responds to chlorpromazine. The methods is lacking whether delirium was assessed immediately before the drug was given, and on day 3 and 7 together with sleep assessment. It is very likely that in this cohort of advanced cancer patients with short survival (table 1, page 15) many patients with sleep disturbances are actually had delirium. In Methods (page 4, third paragraph), the authors stated that “three physicians specialized in palliative care with more than 15 years experience diagnosed sleep disturbances using the American Psychiatric Association diagnostic criteria...etc.”. Did they assess for the presence or absence of delirium also?

Reply 1: We appreciate your thoughtful feedback. We have added some text to address this issue:

Added text (see Page 8, line 128-130):

“In addition, the presence or absence of delirium between day zero (pre-dose) and days three and seven post-dose was diagnosed using DSM-V.”

Please see Reply 2. We have added the exclusion criteria in the Study participants section.

Comment 2: Other inclusion and exclusion criteria should be provided in Methods.

Reply 2: We have revised the relevant text in the Study participants section as follows:

Revised text (see Page 9-10, line 148-159):

“Inclusion criteria of the study were as follows: patients with incurable cancer with difficulty receiving oral administration who were diagnosed with sleep disturbances; informed consent for intravenous chlorpromazine was obtained from these patients. Exclusion criteria were as follows: patients <20 years of age, secondary insomnia attributed to delirium or medications, or patients with psychiatric disorder with communication difficulty, such as dementia. This study was conducted at Kansai Medical University Hospital from May 2018 to December 2020. A total of 1,919 patients with cancer who visited the Department of Palliative Care during this period were consecutively enrolled in this study. Among them, 73 met the inclusion criteria, and of these, 21 met the exclusion criteria. A final total of 52 patients with cancer were included in the study. In this study, compounding cardiac risks were also considered as exclusion criteria, but the patient was not applicable.”

Deleted text:

“This study was conducted at Kansai Medical University Hospital from May 2018 to December 2020. A total of 1,919 cancer patients who visited the Department of Palliative Care during this period were consecutively enrolled in this study. Of the incurable cancer patients diagnosed with sleep disturbances who had difficulty in oral administration, 73 who gave informed consent were treated with intravenous chlorpromazine. This study included 52 patients after excluding 21 patients with mental disorders such as dementia, which would create difficulties in completing the SMHSQ.”

Comment 3: Page 5, second paragraph, line 124 and 125: “1919 cancer patients who visited the department of palliative care during this period were consecutively enrolled in this study. Did you mean screened for the study?”

Reply 3: Yes. Our intended meaning was “screened for this study.”

Changes in the text: None.

Comment 4: Page 7, second paragraph, line 187: “The mean survival period after chlorpromazine treatment was 110 days”. This information is not consistent with table 1 page 15, where about 31 (60%) of patient died within 42 days. Please clarify and reconcile. In addition, please correct the sign of more than or equal to 100 patients in the table 1.

Reply 4: We appreciate your thoughtful feedback. We have revised this text in the Results section (and corrected Table 1) in response to your suggestion:

Revised text (see Page 13, line 226-227):

“The median survival period after chlorpromazine treatment was 34.5 days (range: 1–

790 days).”

Deleted text:

“The mean survival period after chlorpromazine treatment was 110.1 ± 182.6 days.”

We have also double-checked the consistency between the text and table.