Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Details of Study Assessments

Memorial Delirium Assessment Scale (MDAS)

This is a 10-item clinician-rated assessment scale validated for assessment of delirium in cancer patients.[1,2] It examines the level of consciousness, disorientation, memory, recall, attention, disorganized thinking, perceptual disturbance, delusions, psychomotor activity and sleep, assigning a score between 0 to 3, for a total score between 0-30. A score of 13 or higher indicates delirium. This assessment was conducted by the bedside nurse (RN) or research coordinator (RC) at the time of enrollment (RC), time of study medication administration (RN), 2 hour, 4 hour, 8 hour and 24 hour after study medication administration (RN), and then daily until discharge (RC).

Use of Psychotropic Medications

The total dose of neuroleptics during the first 8 hours was calculated based on the concept of haloperidol equivalent daily dose (HEDD), in which 8 mg of parenteral haloperidol is equivalent to 100 mg of parenteral chlorpromazine.[3,4] This concept has been used in multiple studies to examine neuroleptic use.[5,6] We examined the pattern of use of neuroleptics during the first 8 hours, including scheduled HEDD, rescue HEDD, total HEDD, number of rescue doses, and use of chlorpromazine. These data were retrieved from the Medication Administration Record daily by the RC.

Edmonton Symptom Assessment System (ESAS)

ESAS is a symptom battery that has been validated and widely used in different clinical settings, including the acute palliative care unit.[7-9] Because patients were delirious, caregivers were asked by the RC to provide their proxy rating of ESAS daily. It assessed the average symptom intensity of 10 symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well being) over the past 24 hours. Each symptom was assessed using an 11-point numeric rating scale, ranging from 0 (none) to 10 (worst).

Perceived Patient Comfort

After the patient has completed at least 8 hours of observation after receiving the study medication, the RC assessed perceived patient comfort by asking the blinded caregivers and nurses the following question independently: "In my opinion, the patient was more comfortable after the study medication." The response ranged from "strongly agree", "agree", "neutral", "disagree", and "strongly disagree". In this study, "strongly agree" and "agree" were combined for analysis.

Delirium Related Distress

This 12-item questionnaire examines both the recalled frequency of 6 delirium symptoms and associated distress in the rater: disorientation to time, disorientation to place, visual hallucinations, tactile hallucinations, auditory hallucinations, delusional thoughts and psychomotor agitation. It was administered to family caregivers and nurses daily. The score for recalled frequency ranges between 0 and 4, where 0=not present, 1=a little of the time, 2=some of the time, 3=good part of the time, and 4=most or all of the time. The score for distress in the rater related to each delirium symptom also ranges from 0 to 4, where 0=no distress, 1=a little, 2=a fair amount, 3=very much and 4=extremely distressed. This assessment was administered by the RC to both the bedside nurse and caregiver independently on a daily basis. Previous cross sectional studies using this questionnaire found that a caregivers of patients with delirium had high levels of distress.[10]

Communication Capacity

As an exploratory outcome, we also assessed communication capacity as perceived by caregivers and bedside nurses in regard to the patient's ability "to hear me", "to understand what I said" and "to speak to me" over the past 24 hours. Each item was assessed using a 0-10 numeric rating scale that range on 0-10, where 0=not at all and 10=very much. This assessment was administered by the RC to both the bedside nurse and caregiver independently on a daily basis.

Adverse effects

We monitored the respiratory rate at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hour after study medication administration. We also documented the selected adverse effects associated with neuroleptics using the Udvalg for Kliniske Undersogelser (UKU) side effects rating scale. Specifically, we assessed 8 neurologic

symptoms (dystonia, rigidity, hypokinesia/akinesia, hyperkinesia, tremor, akathisia, epileptic seizures, paraesthesias). Each item was assigned a score by the RC from 0 (absent) to 3 (most severe) based on symptom severity of the last 3 days. The UKU questionnaire was administered at baseline and on day 3.[11]

Acute palliative care unit outcomes

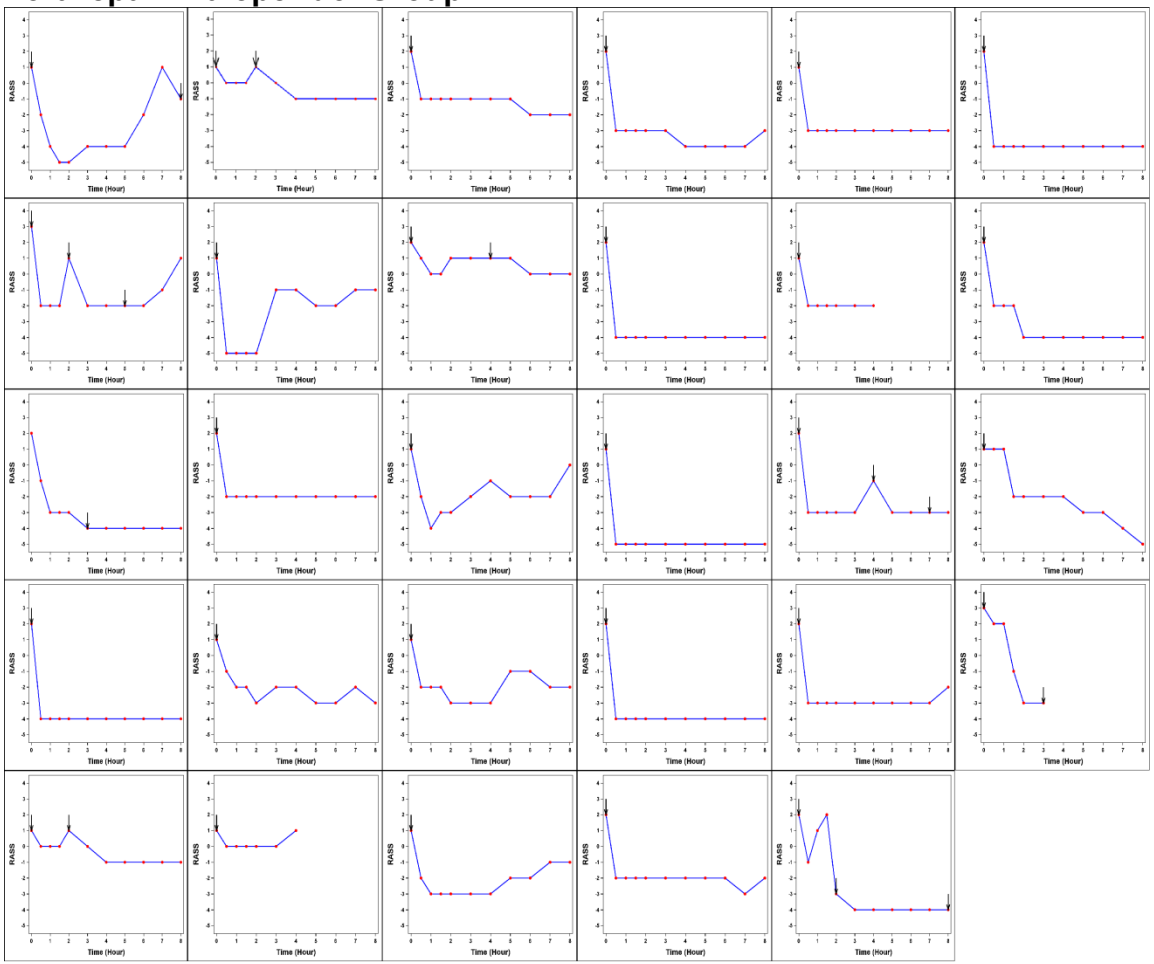
We determined the duration of stay at the acute palliative care unit and whether the patient was discharged alive or dead at the end of admission.

Survival outcome

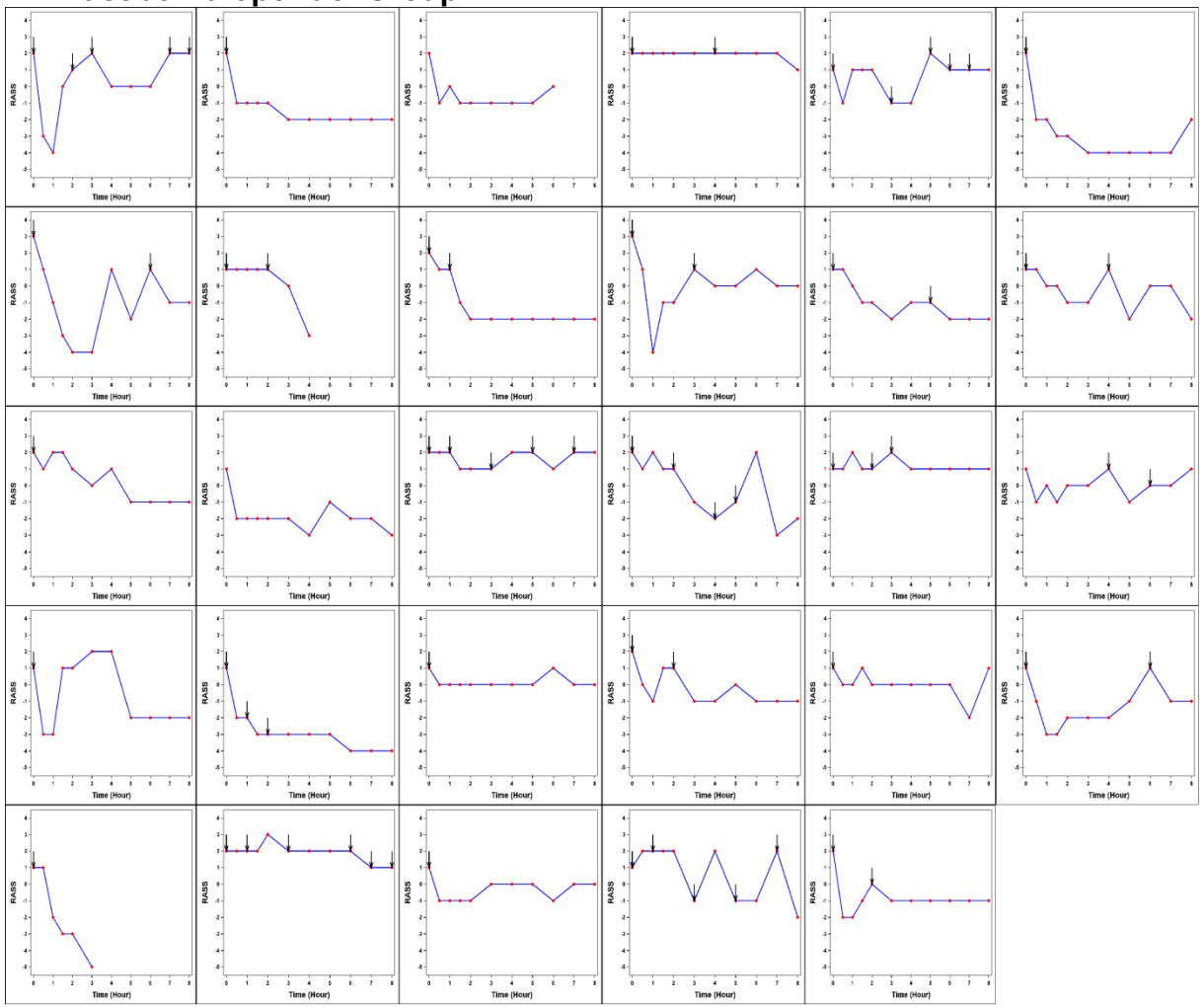
Overall survival was assessed from the time of study medication administration. The date of death or last followup was identified from clinical records and tumor registry.

eFigure 1. Richmond Agitation Sedation Scale (RASS) over the first 8 hours in individual patients. The RASS scores (data markers) are plotted for each patient starting at time 0 (i.e. immediately before blinded study medication administration) over the next 8 hours. The arrows indicate any rescue intravenous haloperidol or chlorpromazine other than the blinded study medication (i.e. lorazepam or placebo) administered during the first 8 hours. (A) Lorazepam/haloperidol group, (B) Placebo/haloperidol group.

A. Lorazepam/Haloperidol Group

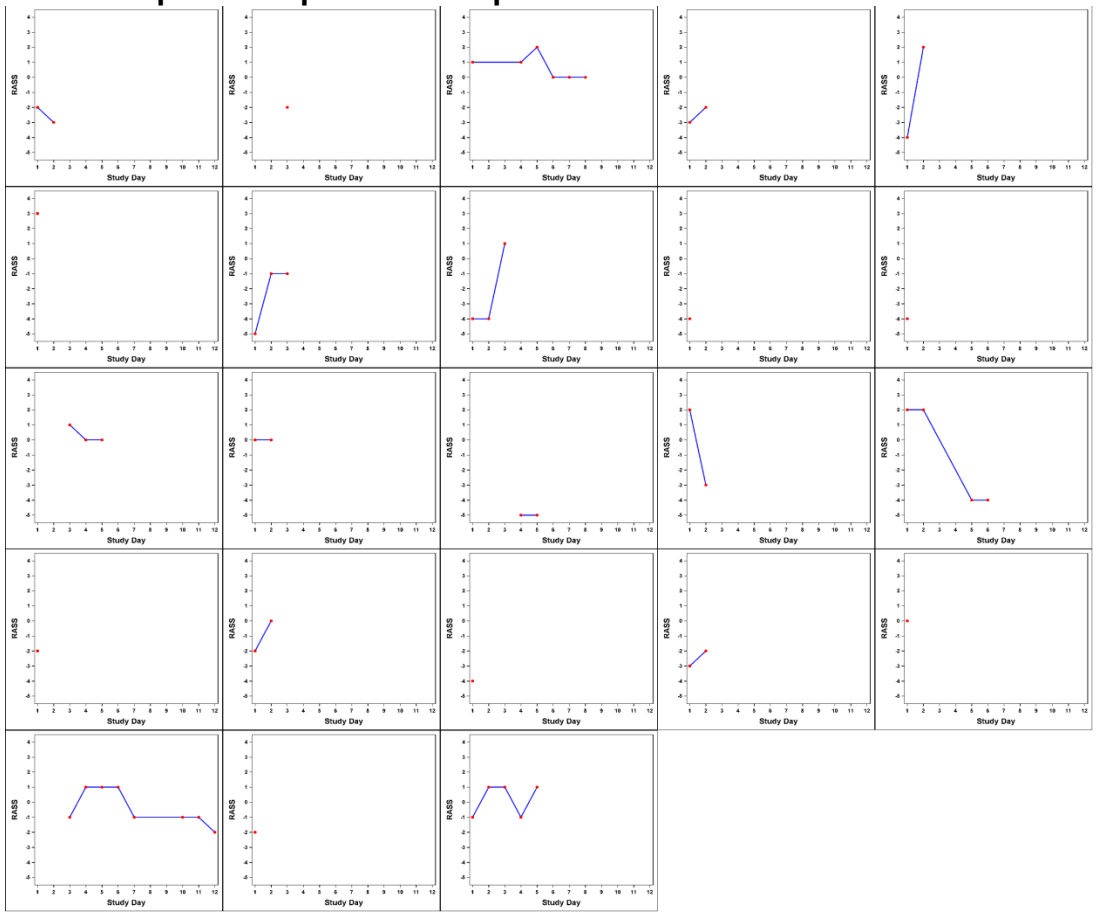


B. Placebo/Haloperidol Group

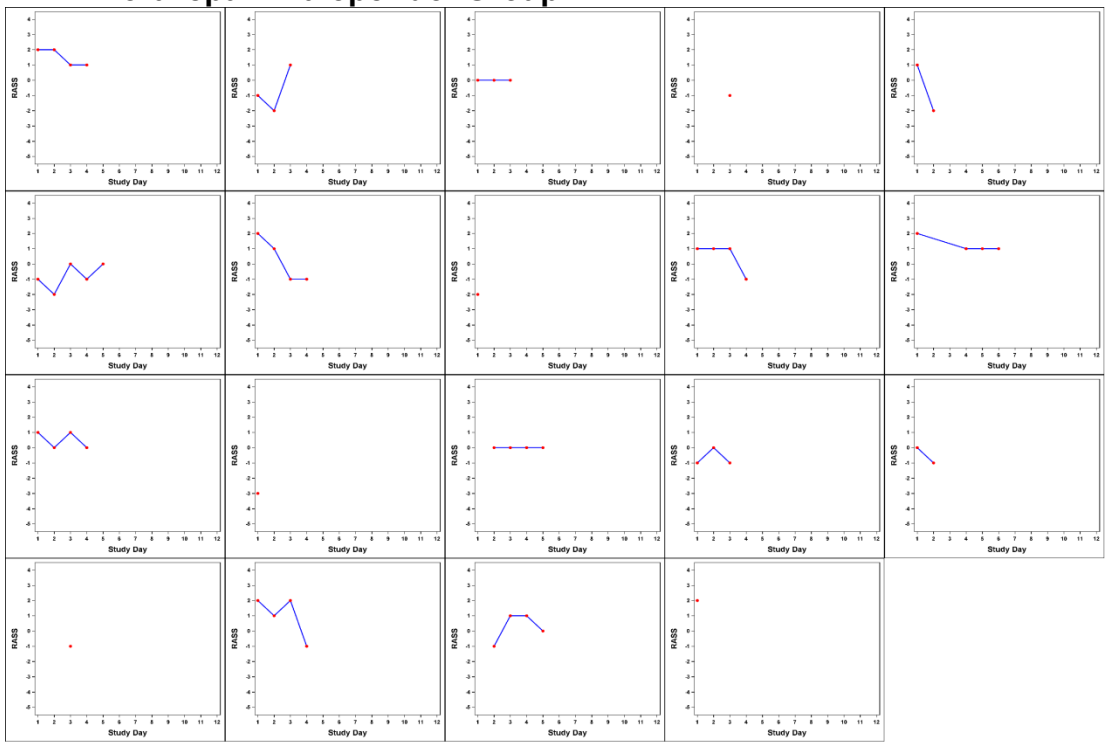


eFigure 2. Richmond Agitation Sedation Scale (RASS) after the first 8 hours in individual patients. The daily RASS scores (data markers) are plotted for each patient starting from the day after blinded study medication until discharge. (A) Lorazepam/haloperidol group, (B) Placebo/haloperidol group. Some patients had no RASS data after the first 8 hours due to death or discharge.

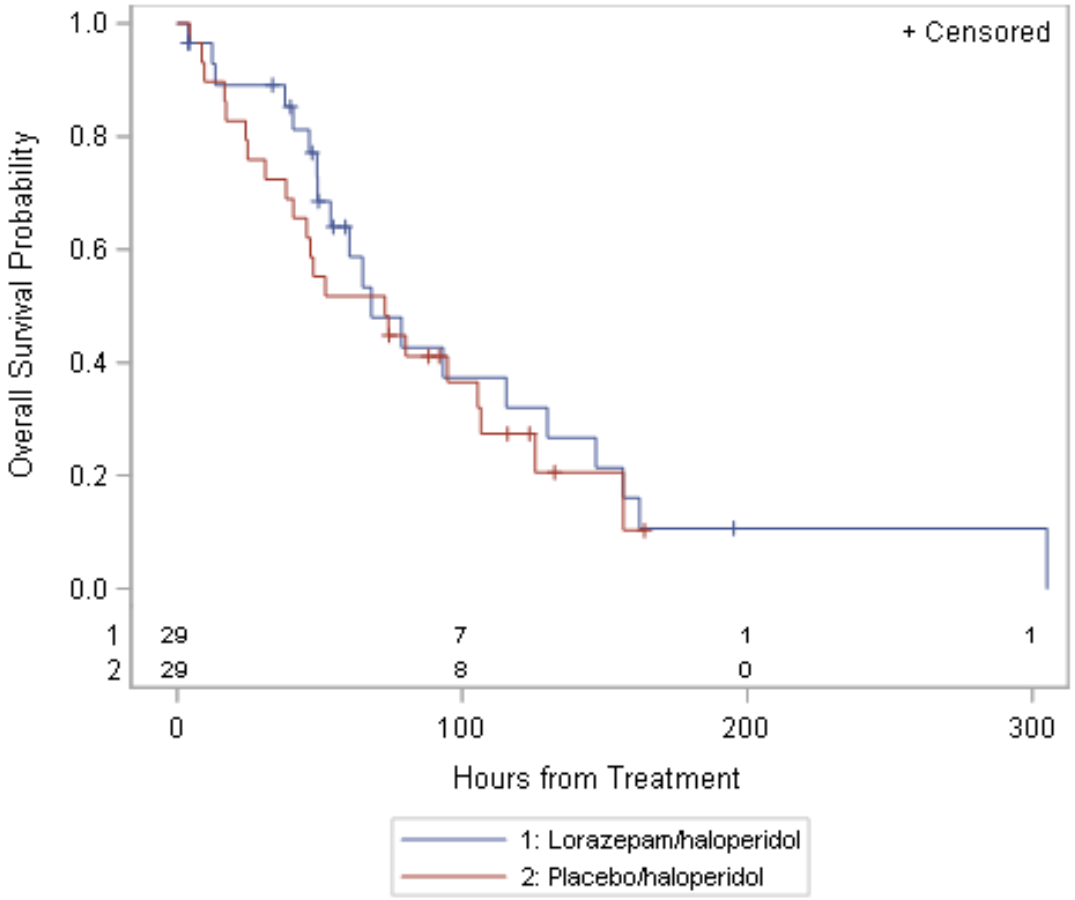
A. Lorazepam/Haloperidol Group



B. Lorazepam/Haloperidol Group



eFigure 3. Overall Survival from Time of Blinded Study Medication Administration. The median survival was 68 h (95% confidence interval [CI], 49 to 130 h) for the lorazepam/haloperidol group and 73 h (95% CI 38, 106 h) for the placebo/haloperidol group, with no significant difference between the two groups (P=0.56, Log rank test). The median followup time was 195 h (95% CI, 55 h to not reached) for the lorazepam/haloperidol group and 132 h (95% confidence interval, 88 h to 164 h) for the placebo/haloperidol group.



eTable 1. Multiple Imputation Analysis for Primary Outcome[a]

	Estimate (95% CI)	Standard Error	P-value
Intercept	-2.44 (-3.11, -1.77)	0.34	<0.001
Treatment Arm (Lorazepam vs Placebo)	-1.60 (-2.55, -0.63)	0.49	0.001

[a] Multiple imputation of missing data was performed for the primary endpoint, RASS change from baseline to 8 hours. We assumed that the data set had a monotone missing pattern, since subjects who were lost to follow-up and missing the primary endpoint were missing all the other subsequent variables, too. We considered a linear model with baseline covariates, age, gender, marital status, education, diagnosis stage, admission reason, Karnosfsky score, Memorial Delirium Assessment Scale at baseline and treatment group. After imputing data for 20 times, linear model was fitted for the effect of treatment on RASS change for each imputed data. Then results from the 20 analyses were combined to generate valid statistical inference about these parameter estimates.

eTable 2. Secondary Outcomes

Outcomes	Lorazepam + Haloperidol		Placebo + Haloperidol		Difference between arms (95% CI)[a]	P-value[b]
Change in caregiver assessment of delirium related distress between baseline and day 1, mean (SD)[c]	N[d]	Mean (95% CI)[a]	N[d]	Mean (95% CI)[a]		
Disorientation to time, frequency	17	-0.41 (-1.41, 0.59)	6	0.33 (-1.25, 1.91)	-0.75 (-2.57, 1.08)	0.58
Disorientation to place, frequency	17	-0.24 (-0.78, 0.33)	5	1.20 (-0.16, 2.56)	-1.44 (-2.59, -0.28)	0.03
Visual hallucinations, frequency	17	-0.35 (-1.08, 0.37)	5	0.60 (-1.82, 3.02)	-0.95 (-2.58, 0.68)	0.48
Tactile hallucinations, frequency	17	-0.12 (-0.52, 0.28)	5	0.80 (-1.89, 3.49)	-0.92 (-2.19, 0.35)	0.68
Auditory hallucinations, frequency	17	-0.12 (-0.89, 0.65)	5	0.80 (-0.82, 2.42)	-0.92 (-2.47, 0.63)	0.18
Delusional thoughts, frequency	17	-0.71 (-1.73, 0.32)	5	1.00 (-1.15, 3.15)	-1.71 (-3.77, 0.36)	0.11
Psychomotor agitation, frequency	17	-0.82 (-1.89, 0.24)	6	-0.50 (-1.95, 0.95)	-0.32 (-2.23, 1.58)	0.64
Disorientation to time, distress	17	-0.71 (-1.71, 0.30)	5	0.20 (-2.89, 3.29)	-0.91 (-3.11, 1.30)	0.26
Disorientation to place, distress	17	-0.71 (-1.21, -0.20)	5	-0.40 (-3.12, 2.32)	-0.31 (-1.70, 1.09)	0.41
Visual hallucinations, distress	17	-0.76 (-1.55, 0.02)	5	0.80 (-0.56, 2.16)	-1.56 (-3.10, -0.03)	0.08
Tactile hallucinations, distress	17	-0.53 (-1.05, -0.01)	5	0.60 (-1.07, 2.27)	-1.13 (-2.28, 0.02)	0.15
Auditory hallucinations, distress	17	-0.41 (-0.93, 0.10)	5	1.00 (-0.52, 2.52)	-1.41 (-2.53, -0.30)	0.02
Delusional thoughts, distress	17	-1.06 (-1.75, -0.37)	5	0.40 (-1.02, 1.82)	-1.46 (-2.85, -0.07)	0.07
Psychomotor agitation, distress	17	-1.00 (-1.95, -0.06)	5	-1.20 (-4.03, 1.63)	0.20 (-1.85, 2.25)	0.81
Change in bedside nurse assessment of delirium related distress between baseline and day 1, mean (SD)[c]						
Disorientation to time, frequency	21	-0.24 (-1.23, 0.76)	15	-0.07 (-0.74, 0.61)	-0.17 (-1.44, 1.10)	0.78
Disorientation to place, frequency	21	0.19 (-0.68, 1.06)	15	-0.07 (-0.94, 0.81)	0.26 (-0.97, 1.48)	0.7
Visual hallucinations, frequency	21	-0.52 (-1.15, 0.10)	15	-0.27 (-1.19, 0.66)	-0.26 (-1.29, 0.77)	0.35
Tactile hallucinations, frequency	21	-0.24 (-0.86, 0.39)	15	-0.47 (-1.40, 0.47)	0.23 (-0.81, 1.27)	0.62
Auditory hallucinations, frequency	21	-0.48 (-1.03, 0.07)	15	-0.53 (-1.37, 0.30)	0.06 (-0.86, 0.98)	>0.99
Delusional thoughts, frequency	21	-0.76 (-1.30, -0.23)	15	0.13 (-0.62, 0.88)	-0.90 (-1.76, -0.03)	0.02
Psychomotor agitation, frequency	21	-0.52 (-1.31, 0.26)	15	-0.13 (-0.97, 0.70)	-0.39 (-1.51, 0.73)	0.36
Disorientation to time, distress	21	-0.33 (-0.82, 0.15)	15	-0.13 (-0.79, 0.52)	-0.20 (-0.97, 0.57)	0.98
Disorientation to place, distress	21	-0.38 (-0.93, 0.17)	15	-0.13 (-0.79, 0.52)	-0.25 (-1.07, 0.57)	0.98
Visual hallucinations, distress	21	-0.38 (-0.85, 0.09)	15	0.07 (-0.38, 0.51)	-0.45 (-1.09, 0.20)	0.19
Tactile hallucinations, distress	21	-0.19 (-0.59, 0.21)	15	0.00 (-0.42, 0.42)	-0.19 (-0.76, 0.38)	0.73
Auditory hallucinations, distress	21	-0.05 (-0.27, 0.18)	15	-0.20 (-0.68, 0.28)	0.15 (-0.31, 0.61)	0.62

Outcomes	Lorazepam + Haloperidol		Placebo + Haloperidol		Difference between arms (95% CI)[a]	P-value[b]
Delusional thoughts, distress	21	-0.38 (-0.87, 0.11)	15	-0.13 (-0.64, 0.37)	-0.25 (-0.94, 0.45)	0.46
Psychomotor agitation, distress	21	-0.48 (-1.26, 0.31)	15	0.07 (-0.73, 0.86)	-0.54 (-1.65, 0.56)	0.44
Change in caregiver assessment of communication capacity, mean (SD)[e]						
Ability to hear	17	-2.82 (-4.61, -1.04)	7	-2.43 (-6.18, 1.52)	-0.39 (-3.60, 2.81)	0.9
Ability to understand	17	-2.59 (-4.57, -0.61)	7	-1.71 (-5.28, 1.95)	-0.87 (-4.30, 2.55)	0.57
Ability to speak	17	-1.94 (-3.53, -0.35)	7	-0.83 (-3.26, 1.60)	-1.08 (-3.75, 1.58)	0.53
Improvement in ability to hear, agree or strongly agree, No. (%)	19	3 (15.8)	19	1 (5.3)	11% (-23%, 43%)	0.60
Improvement in ability to understand, agree or strongly agree, No. (%)	19	3 (15.8)	19	0 (0)	16% (-18%, 47%)	0.23
Improvement in ability to speak, agree or strongly agree, No. (%)	19	1 (5.3)	19	5 (26.3)	-21% (-52%, 13%)	0.18
Change in bedside nurse assessment of communication capacity, mean (SD)[e]						
Ability to hear	21	-1.67 (-3.58, 0.25)	16	-1.31 (-2.95, 0.32)	-0.35 (-2.89, 2.18)	0.69
Ability to understand	21	-1.24 (-2.81, 0.34)	16	-1.25 (-2.59, 0.09)	0.01 (-2.07, 2.10)	0.95
Ability to speak	21	-2.48 (-4.42, -0.53)	16	0 (-1.71, 1.71)	-2.48 (-5.07, 0.12)	0.12
Improvement in ability to hear, agree or strongly agree, No. (%)	22	1 (4.5)	20	2 (10.0)	-5% (-36%, 25%)	0.60
Improvement in ability to understand, agree or strongly agree, No. (%)	22	1 (4.5)	20	2 (10.0)	-5% (-36, 25%)	0.60
Improvement in ability to speak, agree or strongly agree, No. (%)	22	1 (4.5)	20	2 (10.0)	-5% (-36%, 25%)	0.60

Abbreviations: SD, standard deviation

[a] Unless otherwise specified

[b] We compared the change in secondary study outcomes before and after medication administration between groups using 2-tailed Wilcoxon Rank Sum test for continuous variables and 2-tailed Fisher's exact test for categorical variables. All secondary outcomes are considered hypothesis-generating.

[c] This 12-item questionnaire examines both the recalled frequency of 6 delirium symptoms and associated distress in the rater: disorientation to time, disorientation to place, visual hallucinations, tactile hallucinations, auditory hallucinations, delusional thoughts and psychomotor agitation. It was administered to family caregivers and nurses daily. The score for recalled frequency ranges between 0 and 4, where 0=not present, 1=a little of the time, 2=some of the time, 3=good part of the time, and 4=most or all of the time. The score for distress in the rater related to each delirium symptom also ranges from 0 to 4, where 0=no distress, 1=a little, 2=a fair amount, 3=very much and 4=extremely distressed. This assessment was administered by the research coordinator to both the bedside nurse and caregiver independently on a daily basis. Previous cross sectional studies using this questionnaire found that a caregivers of patients with delirium had high levels of distress.[10]

[d] The number of patients with data available for each analysis is shown. The number of patients with missing data varied because of attrition (e.g. death), the specific timing of study assessments and the availability of caregivers/bedside nurses.
[e] As an exploratory outcome, we also assessed communication capacity as perceived by caregivers and bedside nurses in regard to the patient's ability "to hear me", "to understand what I said" and "to speak to me" over the past 24 hours. Each item was assessed using a 0-10 numeric rating scale that range on 0-10, where 0=not at all and 10=very much. This assessment was administered by the RC to both the bedside nurse and caregiver independently on a daily basis.

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