Critical Care

REVIEW

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Haloperidol in treating delirium, reducing mortality, and preventing delirium occurrence: Bayesian and frequentist meta-analyses

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Abstract

Background Although haloperidol is commonly used to treat or prevent delirium in intensive care unit (ICU) patients, the evidence remains inconclusive. This study aimed to comprehensively evaluate the efficacy and safety of haloperidol for delirium treatment and prevention in ICU patients.

Methods We searched MEDLINE, the cochrane central register of controlled trials, EMBASE, ClinicalTrial.gov, and PubMed without language restrictions from database inception to June 27, 2024. We included double-blind randomized controlled trials (RCTs) on haloperidol versus placebo for treating and preventing delirium in adult ICU patients. In addition to frequentist analyses, Bayesian analysis was used to calculate the posterior probabilities of any benefit/harm and clinically important benefit/harm (CIB/CIH). The primary outcomes for delirium treatment were all-cause mortality and serious adverse events (SAEs). For delirium prevention, the primary outcomes included incident delirium, all-cause mortality, and SAEs. The secondary outcomes for efficacy were delirium-or coma-free days, ventilator-free days, length of stay in ICU, length of stay in hospital, and rescue benzodiazepine use. The secondary outcomes for safety were QTc prolongation and extrapyramidal syndrome.

Results We included seven RCTs on delirium treatment (n = 1767) and five on delirium prevention (n = 2509). The Bayesian analysis showed that, compared to placebo for delirium treatment, haloperidol had a 68% probability of achieving CIB (defined as risk difference [RD] < −0.02) in reducing all-cause mortality, a 2% probability of achieving CIH (RD > 0.02) in causing SAEs, and a 78% probability of achieving CIB (RD < −0.02) in reducing the need for rescue benzodiazepine use. The probabilities of haloperidol causing CIH (RD > 0.02) across all other safety outcomes were low (all < 50%). In frequentist analysis on delirium treatment, the pooled estimated RD for haloperidol compared to placebo was -0.05 (−0.09, −0.00; $I^2 = 0\%$) for rescue benzodiazepine use. In Bayesian analysis on delirium prevention, haloperidol had a 12% probability of achieving CIB in all-cause mortality, a 34% probability of achieving CIB in delirium incidence, and a 0% probability of achieving CIB in SAEs. Importantly, haloperidol had a 65% probability of causing

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CIH (risk ratio > 1.1) for QTc prolongation, while the posterior probabilities of achieving CIB across all efficacy outcomes were low (all < 50%). In frequentist analysis on delirium prevention, all primary and secondary outcomes were not statistically significant in frequentist analysis.

Conclusion Our study supported the use of haloperidol for delirium treatment in adult ICU patients, but not for delirium prevention.

Keywords Haloperidol, Delirium, Intensive care unit patients, Bayesian meta-analysis, Mortality

Introduction

Delirium is a prevalent, serious, and potentially fatal acute disturbance of attention and cognition [1, 2]. It affects 30–60% of intensive care unit (ICU) patients on mechanical ventilation and 20–40% of non-ventilated patients [2–6]. Several adverse outcomes have been reported in patients with delirium, including long-term cognitive impairment, longer ventilator use, extended ICU and hospital stays, increased benzodiazepine (BZD) use, impaired daily activity, and higher mortality rates [3, 7–9]. Therefore, there is a critical need to identify effective methods for treating or preventing delirium, ensuring optimal outcomes for ICU patients [6].

Previous studies have examined several pharmacological interventions for delirium management, including haloperidol, dexmedetomidine, ramelteon, and rivastigmine [10, 11]. Although BZDs are commonly used to treat agitation in patients with delirium, such medications have been associated with exacerbating delirium symptoms and increasing mortality [9, 12]. Generally, delirium signals a patient is at heightened risk, but no proven pharmacological interventions to treat delirium exist [13].

The largest RCT (n = 1000) found no significant difference in days alive or out of the hospital at 90 days between haloperidol and placebo. However, a Bayesian re-analysis suggested high probabilities of benefit and low probabilities of harm for haloperidol across outcomes [14, 15]. Importantly, most meta-analyses have used a frequentist framework to synthesize evidence from RCTs, but their findings have been inconsistent [16, 17]. As placebo-controlled RCTs are published, the frequentist meta-analysis can be updated. In addition, to date, no Bayesian meta-analysis has addressed the efficacy and safety of haloperidol in the treatment or prevention of delirium.

To address this knowledge gap, we employed both Bayesian and frequentist meta-analyses to simultaneously evaluate haloperidol for both the treatment and prevention of delirium. Importantly, Bayesian analysis uses probabilities instead of dichotomized conclusions, as seen in frequentist statistics, providing a more nuanced and probabilistic approach to interpreting data. Moreover, we determined the probabilities of any benefit/harm, as well as clinically important benefits/harms (CIBs/CIHs), for key delirium-related outcomes. This dual-method approach can provide more comprehensive results and compensates for the shortcomings of each method. The frequentist method provides traditional effect size estimates and significance testing, while the Bayesian method offers more flexible probabilistic inference and quantification of uncertainty, thereby enhancing the confidence and value of the meta-analysis for physicians regarding the nuanced aspects of haloperidol's efficacy and safety in the treatment and prevention of delirium [18].

Methods

The study protocol was registered with PROSPERO (CRD42024562120). We followed the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) [19], which can be found in Appendix 1.

Eligibility criteria

Eligible studies were double-blinded, randomized controlled trials with a placebo control. We included (i) adult ICU patients (age ≥ 18 years), (ii) adults evaluated for delirium treatment or prevention. We excluded (i) conference abstracts, editorials, case series, observational studies, single-arm pre–post studies, head-to-head design without placebo, and quasi-randomized trials, and (ii) non-ICU patients, patients aged less than 18 years, or studies involving combination therapy with other medication. The route and dosage of haloperidol were not restricted, and rescue medication was allowed.

Data sources and search

Two reviewers independently searched MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, ClinicalTrial.gov, and PubMed without language restrictions from database inception to June 27, 2024. We also searched the gray literature and reviewed the reference lists of the included studies and related systematic reviews [16, 17].

Study selection

Two reviewers independently screened titles, abstracts, and full-text articles. Disagreements were resolved through discussion and, if necessary, by consulting the

corresponding authors. Appendix 2 demonstrates the complete search strategies and appendix 3 shows the reasons for exclusion.

Data extraction and outcome definition

Two reviewers independently extracted the data and discrepancies were resolved by consensus and, when necessary, by consulting the corresponding authors. The primary outcomes of delirium treatment were all-cause mortality and serious adverse event (SAE), whereas the secondary outcomes were delirium- or coma-free days (DCFD), ventilator-free days (VFD), rescue BZD use, length of stay in ICU days, length of stay in hospital days, extrapyramidal syndrome (EPS), and QTc prolongation.

The primary outcomes of delirium prevention were all-cause mortality during study period at longest follow-up, incident delirium, and SAE. The secondary outcomes were length of stay in ICU days, length of stay in hospital days, rescue BZD use, EPS, and QTc prolongation. WebPlot Digitizer (https://apps.automeris.io/wpd/) was used to extract numerical data from the figures. We assessed all outcomes at the maximum follow-up, including all-cause mortality. SAE is defined as an untoward medical occurrence that: (1) Is life-threatening, (2) Requires hospitalization or prolongation of existing hospitalization, (3) Results in persistent or significant disability, or (4) Is considered an important medical event based on medical or scientific judgment. We excluded mortality when calculating SAE. SAE events will only be extracted when they are proactively reported in the study.

Quality assessment

The Cochrane Risk of Bias Assessment Tool (version 2.0) was utilized to evaluate the quality of the RCTs [20]. Two authors independently conducted this assessment, and discrepancies were resolved by consulting the corresponding authors.

Data synthesis

In the Bayesian framework, a generalized linear mixed model was applied. For dichotomous outcomes (e.g., SAE), we calculated the risk difference (RD) and risk ratio (RR), and for continuous outcomes (e.g., length of stay in ICU days), we calculated the mean difference (MD) and ratio of means (ROM). For simplicity, we primarily reported RD and MD. Pooled estimates were calculated with 95% credible intervals (CrI), and quantitative heterogeneity was assessed using the posterior estimates of the heterogeneity parameter (τ) with its 95% CrI. Bayesian meta-analysis provides posterior probabilities that both the primary and secondary outcomes achieve clinically important benefit (CIB) and clinically important harm (CIH). The definitions of thresholds [15] for any benefit, harm, CIB, and CIH were pre-specified in the protocol (see eTable 1).

Except for DCFD and VFD, the cut-off values were defined as follows:

Any benefit: RD < 0, MD < 0, RR < 1, and ROM < 1.

Any harm: RD > 0, MD > 0, RR > 1, and ROM > 1.

CIB: RD < −0.02 (decrease 2%), MD < −1, RR < 0.9, and ROM < 0.9

CIH: RD > 0.02 (increase 2%), MD > 1, RR > 1.1, and ROM > 1.1

For DCFD and VFD, the cut-off values were defined as follows:

Any benefit: MD > 0, ROM > 1.

Any harm: MD < 0, ROM < 1.

CIB: MD > 1, ROM > 1.1

CIH: MD < −1, ROM < 0.9

A Bayesian multilevel model using Stan was performed. Appendix 4 presents the convergence diagnostics and prior distributions. We used weakly informative priors in the Bayesian analyses of all outcomes. These priors were centered on no difference and included all plausible effect sizes to ensure that the data predominantly informed the results while preventing extreme inferences. The prior distributions were selected based on their suitability for each outcome type, with normal distributions for intercepts and Cauchy distributions for heterogeneity parameters, both parameterized to allow for reasonable uncertainty while avoiding overly strong assumptions. For example, for risk difference outcomes, we specified a Normal prior for the intercept (location = 0, scale = 0.2), with 95% of the prior probability mass within [−0.39, 0.39], and a Cauchy prior for heterogeneity (location = 0, scale = 0.2), with 95% probability mass within [−2.54, 2.54]. Four Markov chains are implemented. There were 50,000 iterations per chain, and the first 20,000 iterations for each chain were discarded as warm-up. Convergence was assessed by visual inspection of the trace and autocorrelation plots of the key parameters for each analysis. For both delirium treatment and prevention, a sensitivity analysis using a beta-binomial model was conducted for the primary outcomes within the Bayesian analysis. The beta-binomial model allows for more flexible modeling of between-study variability in the event rates, particularly when there is uncertainty in the event probabilities.

In the frequentist framework, a random-effects meta-analysis was conducted using restricted maximum likelihood. Pooled estimates were reported with 95% confidence intervals (CI), and quantitative heterogeneity was assessed using the I^2 statistic, and an $I^2 > 50\%$ indicates substantial heterogeneity between studies. A continuity correction of 0.5 was applied for zero events in one arm, while studies with zero events in both arms were excluded from the analysis. All analyses were

conducted using the statistical software R, version 4.2.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the *brms*, *meta*, *rjags*, and *metafor* R packages [21–24].

Results

After completing the systematic search and screening procedures, 82 articles were considered for full-text review, of which 12 met the eligibility criteria (Fig. 1). Among the 12 studies, 7 were on delirium treatment [14,

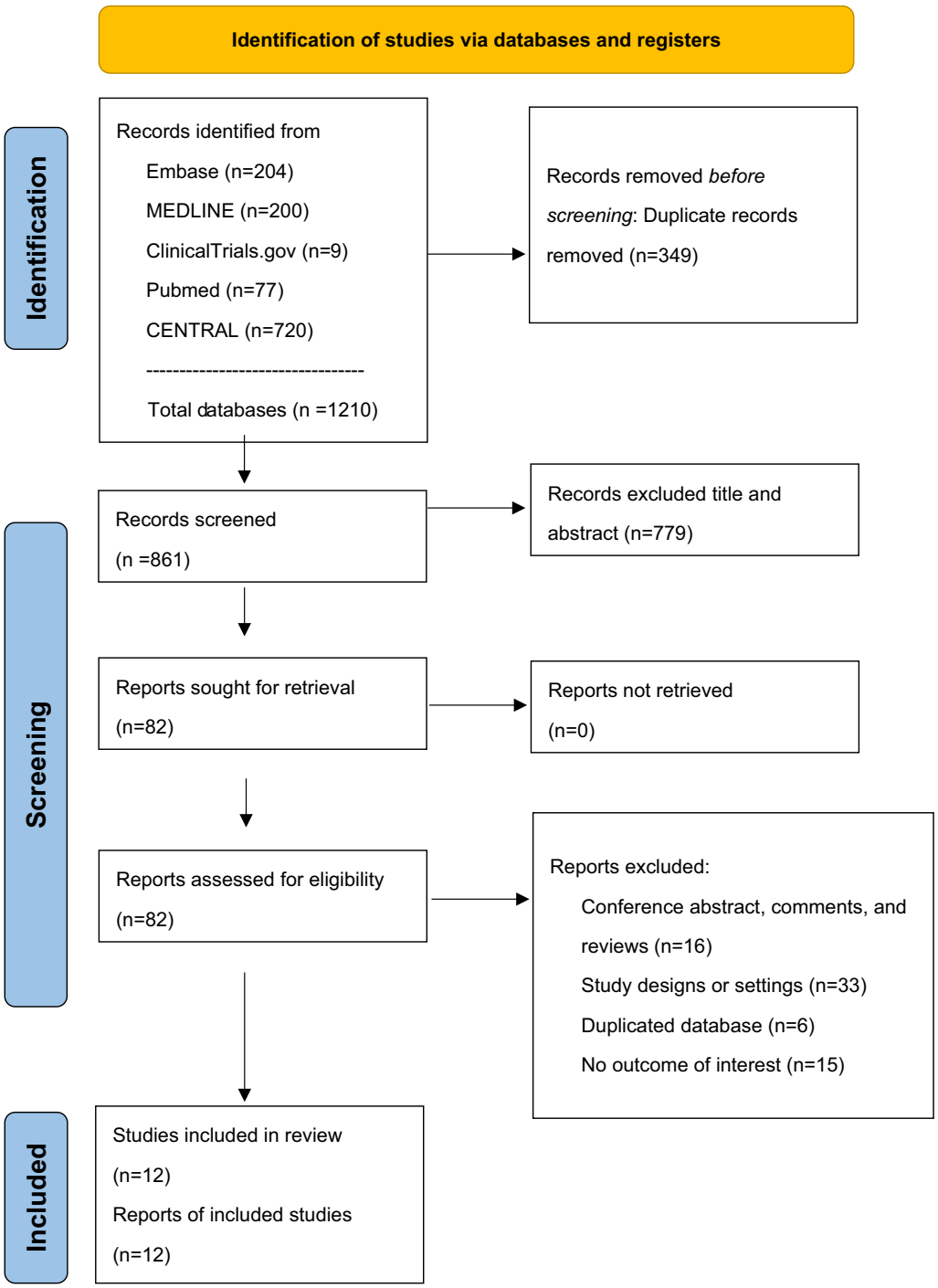

Fig. 1 Flow chart of study selection. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n7

25–30] and 5 were on delirium prevention [31–35]. In the RCTs on delirium treatment, one study [29] reported that 90% of participants exhibited delirium on day 1, and another study [27] included participants who had abnormal levels of consciousness, and 83% of participants experienced delirium or coma on day 1. Therefore, these two studies were appropriately included in the treatment of delirium category. Among the RCTs on delirium prevention, one trial included patients with subsyndromal delirium [32], while the remaining trials involved ICU patients without delirium.

Demographic characteristics

Overall, 1767 participants (mean age: 66.87 years [standard deviation: 5.25]; average male percentage range: 53.3–68.5%) were included for delirium treatment, and 2509 participants (mean age: 67.20 years [4.42]; average male percentage range: 55.9–74.4%) were included for delirium prevention. The details of the characteristics of the included studies are presented in eTable 2.

Delirium treatment

Figure 2 presents the primary outcomes of delirium treatment using Bayesian meta-analysis, while Fig. 3 presents the results of frequentist meta-analysis. For all-cause mortality, we found four trials (4/7) with low ROB (eFigs. 1 and 10). In Bayesian analysis, haloperidol had an RD of −0.03 (95% CrI: −0.09, 0.03) compared with placebo. We found an 86% probability of any benefit of haloperidol and a 68% probability of CIB of haloperidol. In frequentist analysis (Fig. 3A, B), no statistically significant difference was found (RD: −0.03, 95% CI: −0.08, 0.01, $I^2 = 0\%$).

For SAEs, we found four trials (4/6) with low ROB (eFigs. 2 and 11). In Bayesian analysis, haloperidol had an RD of −0.01 (95% CrI: −0.03, 0.02) compared with placebo. We found only a 2% probability of CIH of haloperidol. In frequentist analysis (Fig. 3A, B), no statistically significant difference was found (RD: −0.01, 95% CI: −0.02, 0.01, $I^2 = 0\%$).

The secondary outcomes are presented in Table 1 and Fig. 3, namely rescue BZD use, EPS, QTc prolongation, DCFD, VFD, length of stay in ICU days, and length of stay in hospital days. Few studies reported on secondary outcomes had low ROB (eFigs. 3–9, 12–18). In Bayesian analysis, haloperidol had an RD of −0.05 (95% CrI: −0.14, 0.04) for rescue BZD use compared with placebo. We found a 90% probability of any benefit and a 78% probability of CIB for haloperidol in reducing rescue BZD use. For the other secondary outcomes, the probabilities of CIB and CIH were low (all < 50%). In frequentist analysis, no statistically significant differences were found between the haloperidol and placebo in most secondary outcomes. However, for rescue BZD use, haloperidol was associated with a lower rescue BZD use compared with placebo (an RD of −0.05, 95% CI: −0.09, −0.00; $I^2 = 0\%$).

Delirium prevention

Table 2 presents the primary and secondary outcomes of delirium prevention using Bayesian meta-analysis,

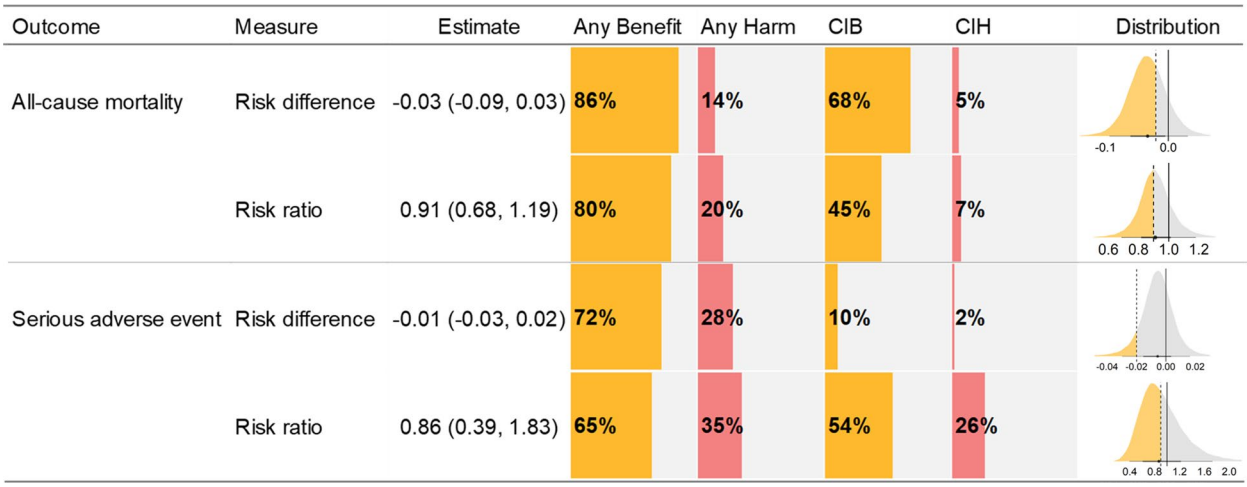

Fig. 2 Posterior probability of haloperidol versus placebo for delirium treatment on the primary outcomes. The distribution chart on the right, yellow represents the probability of exceeding the clinical important benefit, while pink represents the probability of being below the clinical important benefit. For the values on the left, yellow represents the benefit values, and pink represents the harm values. Abbreviation: CIB = clnically imporant benefit; CIH = clinically imporant harm. [a]Dotted line indicates clinical important benefit, and solid line indicates no difference. [b]The cut-off point for clinically important benefit is −0.02 for risk difference and 0.9 for risk ratio, while the cut-off point for clinically important harm is 0.02 for risk difference and 1.1 for risk ratio

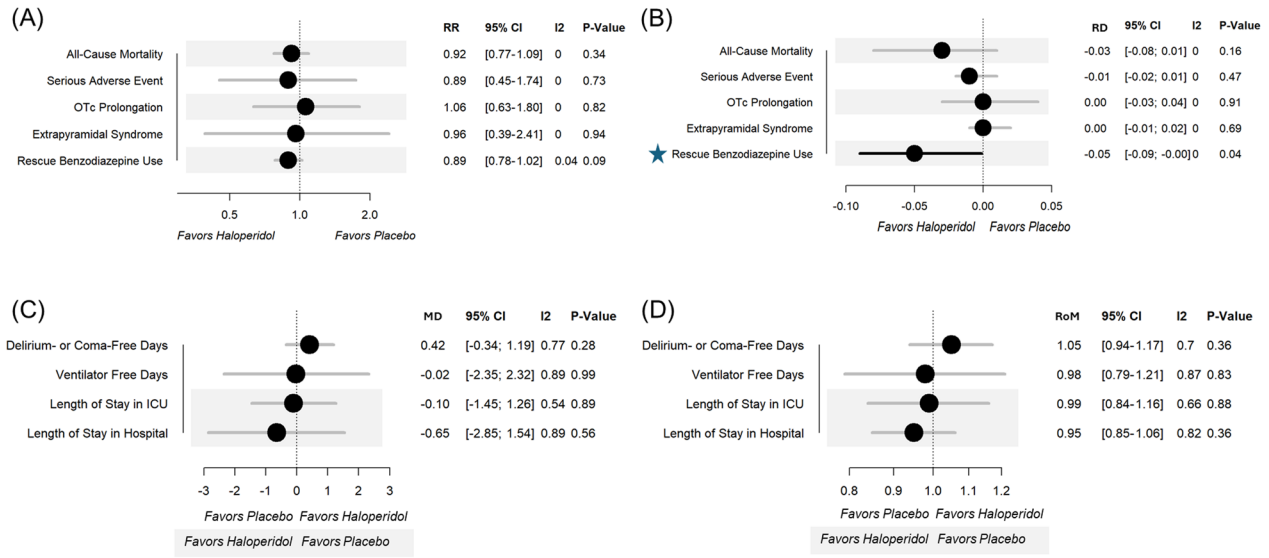

Fig. 3 Haloperidol for delirium treatment using frequentist meta-analysis. Dichotomous outcomes of delirium treatment presented as **A** Risk ratio **B** Risk difference. Continuous outcomes of delirium treatment presented as (**C**) mean difference (day) (**B**) Ratio of means. Abbreviation: CI = confidence interval; ICU = intensive care unit; MD = mean difference; RD = risk difference; RoM = ratio of means; RR = Risk ratio. [a]Interpret grey-shaded results according to the grey-shaded directional indications

Table 1 Posterior probability of haloperidol for delirium treatment for the secondary outcomes

Outcome	Measure	Estimate	Any benefit	Any harm	CIB	CIH
Rescue BZD use	Risk difference	−0.05 (−0.14,0.04)	90%	10%	78%	5%
	Risk ratio	0.89 (0.68, 1.16)	88%	12%	56%	4%
Extrapyramidal syndrome	Risk difference	0.00 (−0.05, 0.05)	46%	54%	13%	15%
	Risk ratio	0.01 (0.39, 2.67)	49%	51%	4%	43%
QTc prolongation	Risk difference	0.00 (−0.06, 0.07)	47%	53%	20%	24%
	Risk ratio	1.04 (0.53,2.02)	44%	56%	32%	43%
Deliriu- or coma-free days	Mean difference	0.44 (−0.61, 1.51)	83%	17%	11%	1%
	Ration of means	1.05 (0.89, 1.23)	79%	21%	24%	3%
Ventilator-free days	Mean difference	−0.00 (−3.09, 3.09)	50%	50%	22%	22%
	Ration of means	0.97(0.70, 1.38)	44%	56%	19%	26%
Length of stay in ICU days	Mean difference	−0.06 (−1.83,2.18)	57%	43%	13%	13%
	Ration of means	0.99 (0.78, 1.29)	55%	45%	17%	16%
Length of stay in hospital days	Mean difference	−0.68 (−3.87, 2.14)	68%	32%	37%	10%
	Ration of means	0.94 (0.78, 1.12)	77%	23%	26%	3%

BZD, benzodiazepine; CIB, clnically imporant benefit; CIH, clinically imporant harm; ICU, intensive care unit

[a] For the outcomes of rescue BZD use, extrapyramidal syndrome, QTc prolongation, the cut-off value of clnically imporant benefit is − 0.02 for risk difference and 0.9 for risk ratio

[b] For the outcomes of rescue BZD use, extrapyramidal syndrome, QTc prolongation, the cut-off value of clnically imporant harm is 0.02 for risk difference and 1.1 for risk ratio

[c] For the outcomes of delirium- or coma-free days and ventilator-free days, the cut-off value of clnically imporant benefit is 1 (day) for risk difference and 1.1 for ratio of means

[d] For the outcomes of delirium- or coma-free days and ventilator-free days, the cut-off value of clnically imporant harm is −1 (day) for risk difference and 0.9 for ratio of means

[e] For length of stay in ICU/hospital,, the cut-off value of clnically imporant benefit is −1 (day) for risk difference and 0.9 for ratio of means

[f] For length of stay in ICU/hospital,, the cut-off value of clnically imporant harm is 1 (day) for risk difference and 1.1 for ratio of means

Table 2 Posterior probability of haloperidol for delirium prevention for the primary and the secondary outcomes

Outcome	Measure	Estimate	Any Benefit	Any Harm	CIB	CIH
Mortality	Risk difference	−0.01 (−0.03, 0.02)	70%	30%	12%	4%
	Risk ratio	0.97 (0.63, 1.39)	56%	44%	29%	22%
Delirium Incidence	Risk difference	−0.01 (−0.09, 0.08)	57%	43%	34%	23%
	Risk ratio	0.96 (0.69, 1.30)	59%	41%	28%	16%
Serious adverse event	Risk difference	0.00 (−0.01, 0.01)	38%	62%	0%	0%
	Risk ratio	0.94 (0.35, 2.60)	55%	45%	47%	38%
Rescue BZD use	Risk difference	−0.01 (−0.15, 0.12)	56%	44%	41%	30%
	Risk ratio	0.97 (0.56, 1.58)	56%	44%	33%	25%
Extrapyramidal syndrome	Risk difference	−0.00 (−0.04, 0.02)	60%	40%	8%	4%
	Risk ratio	0.83 (0.37, 1.96)	69%	31%	59%	23%
QTc prolongation	Risk difference	0.01 (−0.02, 0.05)	23%	77%	3%	26%
	Risk ratio	1.21 (0.70, 2.16)	22%	78%	12%	65%
Length of stay in ICU days	Mean difference	−0.20 (−0.79, 0.31)	80%	20%	1%	0%
	Ration of means	0.96 (0.88, 1.05)	85%	15%	5%	1%
Length of stay in hospital days	Mean difference	−0.03 (−1.77, 1.94)	54%	46%	10%	4%
	Ration of means	0.99 (0.86, 1.15)	55%	45%	6%	6%

BZD, benzodiazepine; CIB, clnically imporant benefit; CIH, clinically imporant harm; ICU, intensive care unit

[a] For the outcomes of motality, delirium incidence, serious adverse event, rescue BZD use, extrapyramidal syndrome, QTc prolongation, the cut-off value of clnically imporant benefit is − 0.02 for risk difference and 0.9 for risk ratio, and the cut-off value of clnically imporant harm is 0.02 for risk difference and 1.1 for risk ratio

[b] For length of stay in ICU/hospital,, the cut-off value of clnically imporant benefit is −1 (day) for risk difference and 0.9 for ratio of means

[c] For length of stay in ICU/hospital,, the cut-off value of clnically imporant harm is 1 (day) for risk difference and 1.1 for ratio of means

while eFig. 35 presents the results of frequentist meta-analysis. For all-cause mortality, we found three trials (3/5) with low ROB (eFigs. 19 and 27). In Bayesian analysis, haloperidol had an RD of −0.01 (95% CrI: −0.03, 0.02) with a 12% probability of achieving CIB. For delirium incidence, we found three trials (3/5) with low ROB (eFigs. 20 and 28). Haloperidol had an RD of −0.01 (95% CrI: −0.09, 0.08) with a 34% probability of achieving CIB. For SAEs, we found three trials (3/5) with low ROB (eFigs. 21 and 29). Haloperidol had an RD of 0.00 (95% CrI: −0.01, 0.01) with a 0% probability of achieving CIB. In frequentist analysis, there were no statistically significant differences between haloperidol and placebo in all primary outcomes.

For secondary outcomes, namely rescue BZD use, EPS, QTc prolongation, length of stay in ICU days, and length of stay in hospital days, the quality assessment showed few studies had low ROB (eFig. 22–25, 30–33). In Bayesian analysis, the probabilities of CIB and CIH for all secondary outcomes were low (all < 50%). Notably, haloperidol had an RR of 1.21 (95% CrI: 0.70, 2.16) for QTc prolongation compared with placebo, with a 65% probability of CIH. In frequentist analysis, there were no statistically significant differences between the haloperidol and placebo in all secondary outcomes.

The forest plots for each outcome using the frequentist analysis (eFigs. 36–69) and the Bayesian analysis (eFigs. 70–103) are included in the supplementary data.

Sensitivity analyses

Finally, the results of sensitivity analysis of beta-binomial model showed similar findings on the primary outcomes of delirium treatment and prevention (eTable 3).

Discussion

Principal findings

For delirium treatment with haloperidol versus placebo, we found moderate posterior probabilities of achieving CIB on all-cause mortality and low posterior probabilities of causing SAEs. In addition, we also found a high posterior probability of achieving CIB on rescue BZD use. Regarding other safety outcomes, we found low posterior probabilities of causing CIH. When using haloperidol for delirium prevention, we found low posterior probability of achieving CIB on all-cause mortality, delirium incidence, and SAEs.

However, we found a high posterior probability of causing CIH on QTc prolongation. Given the high probability of any benefit on mortality, low probability of harm, and high probability of less rescue BZD use, the use of

haloperidol for treatment of delirium was supported. However, the efficacy and safety of prophylactic haloperidol for delirium prevention is not supported by the findings of this study.

Comparison with other studies

In our study, the Bayesian analysis suggested that haloperidol for delirium treatment in ICU patients had high probabilities and moderate probabilities of achieving any benefits and CIB on all-cause mortality. A previous meta-analysis with five placebo-controlled RCTs [16] favored haloperidol in decreasing all-cause mortality, although the results were not statistically significant. Compared with this meta-analysis [16], we included two additional placebo-controlled RCTs [27, 29]. The mechanisms of mortality in ICU patients with delirium are complex and multifaceted; thus, several potential reasons for haloperidol-associated lower mortality need to be considered. At the molecular level, in vitro studies have demonstrated the anti-inflammatory effects of haloperidol [36, 37]. This effect may mitigate the cytokine storm in critically ill patients, potentially antagonizing multiple pathways of delirium and reducing the risk of mortality [34, 38]. Second, haloperidol was associated with reduced BZD use in ICU patients with delirium. Although BZDs can be used to manage agitation, anxiety, and insomnia, they may exacerbate delirium and increase mortality among ICU patients with delirium [9, 12]. Therefore, haloperidol might have resulted from less rescue BZD administration. Third, we also found an approximately 80% probability for any benefit of haloperidol versus placebo for the outcome of DCFD. Previous studies have shown that the delirium duration is a strong predictor of 30-day and 2-year death [39, 40].

Results of both frequentist and Bayesian analyses did not support the use of prophylactic haloperidol in ICU patients to prevent major delirium-related outcomes, including all-cause mortality, incident delirium, and SAEs. These results aligned with the findings of a previous meta-analysis within the frequentist framework [41]. Prophylactic haloperidol for delirium prevention did not achieve CIB with at least more than 50% posterior probability for any of the outcomes we measured. Importantly, prophylactic haloperidol for delirium prevention demonstrated a 65% posterior probability of causing CIH on QTc prolongation.

Our study showed that, at the population level, there was no significant difference in the risk of SAE, EPS, and QTc prolongation among ICU patients treated with haloperidol compared with those treated with placebo. These findings were consistent with those of a previous meta-analysis [41]. A systematic review of 34 clinical trials indicated that individuals who received cumulative doses of at least 100 mg haloperidol intravenously or exhibited a QTc interval > 500 ms were considered at a relatively higher risk of QTc prolongation [42]. In our study, the majority of the included RCTs utilized intravenous haloperidol at relatively lower doses, ranging from 1.5 to 7.5 mg/day regularly, or with a maximum of 24 mg/day [14, 26, 28–35]. Studies involving oral or intramuscular routes did not exceed 30 mg/day [25, 27]. Indeed, in our study, neither frequentist nor Bayesian analyses suggested that haloperidol was associated with a higher risk of EPS than that of the placebo.

Limitations

The present study had several limitations. First, there are few studies we included with low risk of bias. Second, the results are limited by few patients making the estimates uncertain. Furthermore, owing to the limited number of studies included, meta-regression and subgroup analyses were not performed. Third, the rescue medications used in different RCTs varied, including not only BZD but also other medication such as antipsychotics, fentanyl, propofol, clonidine, morphine, and dexmedetomidine. With the limited available data, we could only evaluate the risk of rescue BZD use. However, these rescue medications could potentially affect outcomes. I would also include that many studies allow rescue haloperidol meaning diluting a possible potential effect. For example, 20% of patients received open-label antipsychotics in the MIND-USA trial [26], meaning a potential difference could be difficult to find if 1 of 4 in the placebo group might have received haloperidol. Fourth, variations in the administration route and haloperidol dose, as well as heterogeneity in the characteristics of ICU patients (such as underlying diseases, medical/surgical status, ventilator usage, initial severity of delirium, and age), may impede the comparability of outcomes. Fifth, we only included RCTs with critically ill patients in the ICU; therefore, our results cannot be extrapolated to patients with less severe disease. Sixth, there are two RCTs [27, 29] considered as treatment trials, in which only 90% and 83% of participants, respectively, had delirium at the start of the trial. Thus, the results of treatment could be mild overestimated. Seventh, since we are unable to determine the length of hospital stay for the deceased cases with the limited available data, the hospital/ICU stay outcomes may be influenced by these mortality cases (for example, if patients die shortly after being admitted to the ICU, it would reduce the average ICU stay duration). Eighth, two studies did not provide tools for assessing delirium, and both were evaluated as having a high risk of bias because they had more than three domains rated as "some concerns." Lastly, when there is significant heterogeneity

between studies, the results of Bayesian analysis may be greatly affected [18].

Implications and conclusions

Delirium is common, lethal, and expensive condition occurring in ICU patients. Our study provides insights to physicians regarding the nuanced aspects of haloperidol efficacy and safety in this critically ill population. For clinical practice, we suggest that, at the population level, haloperidol for delirium treatment is associated with high probabilities of achieving any benefit on all-cause mortality, moderate probabilities of achieving CIB for these outcomes, high probabilities of achieving CIB for rescue BZD use, and low probabilities of causing CIH across all safety outcomes. It can be used on patients with delirium within a reasonable dosage range. However, there is no robust evidence to support the use of prophylactic haloperidol for delirium prevention. Future studies are required to investigate the predictive factors of both benefit and harm in relation to delirium-related outcomes. In addition, the homogeneity of participants can be increased, such as including only heart surgery patients, stroke patients, or pneumonia patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05342-6.

Additional file1

Author contributions

Tien-Wei, Hsu and Shu-Li Cheng contributed equally to this work as first authors. Yu-Kang Tu and Chih-Sung Liang contributed equally to this work and are joint last/corresponding authors. Chih-Sung Liang, Tien-Wei Hsu, and Yu-Kang Tu conceived and designed the study. Tien-Wei Hsu, Shu-Li Cheng, Chia-Ling Yu, Chih-Wei Hsu, and Ping-Tao Tseng selected the articles, extracted the data, and assess the risk of bias. Chia-Ling Yu did the systemic search. Tien-Wei Hsu and Chih-Sung Liang wrote the first draught of the manuscript. Jia-Ru, Li, Trevor Thompson, Andre F. Carvalho, Brendon Stubbs, Fu-Chi Yang, Yu-Kang Tu interpreted the data and contributed to the writing of the final version of the manuscript. Chih-Sung Liang and Tien-Wei Hsu have accessed and verified the data. Chih-Sung Liang and Yu-Kang Tu were responsible for the decision to submit the manuscript. All authors confirmed that they had full access to all the data in the study and accept responsibility to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

Not required; analysis of aggregated identified clinical trial data.

Competing interests

The authors declare no competing interests.

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