Journal of Critical Care 50 (2019) 280–286

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Haloperidol for the management of delirium in adult intensive care unit patients: A systematic review and meta-analysis of randomized controlled trials

Yazan Zayed [a,*], Mahmoud Barbarawi [a], Babikir Kheiri [a], Momen Banifadel [b], Tarek Haykal [a], Adam Chahine [a], Laith Rashdan [a], Ahmed Aburahma [a], Ghassan Bachuwa [a], Elfateh Seedahmed [c]

[a] Department of Internal Medicine, Hurley Medical Center, Michigan State University, Flint, MI, United States
[b] Internal Medicine Department, University of Toledo, Toledo, OH, United States
[c] Pulmonary and Critical Care Departments, Hurley Medical Center, Michigan State University, Flint, MI, United States

ARTICLE INFO

Keywords:
Haloperidol
ICU
Delirium
Meta-analysis
Critically ill patients

ABSTRACT

Purpose: Delirium commonly presents as a complication in critically ill patients. Our aim is to perform a meta-analysis investigating the role of haloperidol versus placebo in management (treatment and prophylaxis), of delirium in intensive care unit (ICU).

Materials and methods: Our study is a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing haloperidol versus placebo for treatment and/or prophylaxis of ICU-related delirium.

Results: Six RCTs representing 2552 patients. There was no significant difference between haloperidol and placebo-treated patients in short-term all-cause mortality (risk ratio [RR] 0.96; 95% confidence interval [CI] 0.81–1.14; P = 0.67), incidence of delirium (RR 0.93; 95% CI 0.65–1.34; P = 0.70), ICU length of stay (Mean difference [MD] 0.00 days; 95% CI -0.82-0.83; P = 0.99), or delirium/coma-free days (MD 0.09; 95% CI -0.05-0.24; P = 0.21). Haloperidol was not associated with increased risk for serious adverse events (RR 0.65; 95% CI 0.23–1.88; P = 0.43), QTc prolongation (RR 0.87; 95% CI 0.63–1.19; P = 0.38), or extrapyramidal symptoms (RR 0.84; 95% CI 0.57–1.23; P = 0.37).

Conclusion: Among critically ill patients, haloperidol administration compared with placebo does not significantly affect short-term mortality, incidence of delirium, ICU length of stay, or delirium or coma-free days. Additionally, there was no increased risk of adverse events.

1. Introduction

Delirium, a syndrome of acute brain dysfunction, is a common complication in patients undergoing treatment in the intensive care unit (ICU). It is characterized by a daily fluctuating symptoms of confusion, inattention, and consciousness disturbances [1]. The underlying cause of delirium is often multifactorial, and may be related to neurotransmitter pathway alterations, cerebral oxygen deprivation, and increased cerebral inflammatory cytokines [2-4]. In the ICU, the mean incidence of delirium is about 30% as shown in a recent systematic review [5], Of note, ICU patients have greater number of risk factors associated with ICU treatment, with patients averaging 11 delirium-associated risk factors [6].

ICU-related delirium is associated with poor clinical outcomes, including prolonged ICU and hospital length of stay (LOS), development of post-ICU cognitive impairment, and increased health-care costs [7-12]. Current guidelines recommend the early instillation of non-pharmacological strategies for the prevention and treatment of ICU-associated delirium, such as early mobilization, avoidance of excess sedation and benzodiazepines, reorientation, as well as the use of eyeglasses and hearing aids [13].

Haloperidol is a typical antipsychotic with antidopaminergic, anticholinergic, and potential immunomodulatory properties. Use of haloperidol for the management of delirium has previously demonstrated beneficial outcomes in non-critically ill patients, however, its role in ICU patients is controversial [4,14-16]. Therefore, we conducted a meta-analysis of all randomized controlled trials (RCTs) in order to

* Corresponding author.
E-mail address: yzayed1@hurleymc.com (Y. Zayed).

https://doi.org/10.1016/j.jcrc.2019.01.009
0883-9441/

evaluate the efficacy and safety of haloperidol regarding management of delirium in ICU patients in comparison to placebo.

2. Methods

2.1. Study design and data sources

Our study is a systematic review and meta-analysis which was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement [17]. The literature search and study selection were conducted independently by two reviewers (A.A. and L.R.). Any discrepancy was solved by a consensus with a third reviewer (Y.Z.). We systematically searched 3 electronic databases: PubMed, Cochrane Library, and Embase from inception through October 25th, 2018 using the following Mesh terms: "Haloperidol", "antipsychotic", "critically ill", "ICU", "intensive care unit", "critical ill", "delirium", "coma". References of relevant articles were reviewed for possible eligibility. Any discrepancy was solved via a consensus with a third reviewer (Y.Z.). Articles were first screened by title and abstract, and the full text of eligible studies were reviewed before exclusion. The search process is detailed in Fig. 1.

2.2. Selection criteria and data extraction

Only RCTs were eligible for inclusion in our study. We included trials that compared haloperidol versus placebo for the management, both treatment and prophylaxis, of delirium in ICU patients. Before-and-after treatment trials, cohort studies, and retrospective studies were excluded.

A predefined table was constructed by the authors for data extraction which was done by two reviewers separately and independently (M.B. and M.Ba.). Any discrepancy was discussed and resolved with a third reviewer (Y.Z.). Authors of included studies were contacted for missing data.

2.3. Quality assessment

Quality assessment for the included RCTs was performed using the Cochrane Collaboration's tool to assess the risk of bias. We assessed the included RCTs for random sequence generation, allocation concealment, blindness of participants and health-care personnel, blindness of outcome assessment, incomplete outcome data, selective reporting, and other biases.

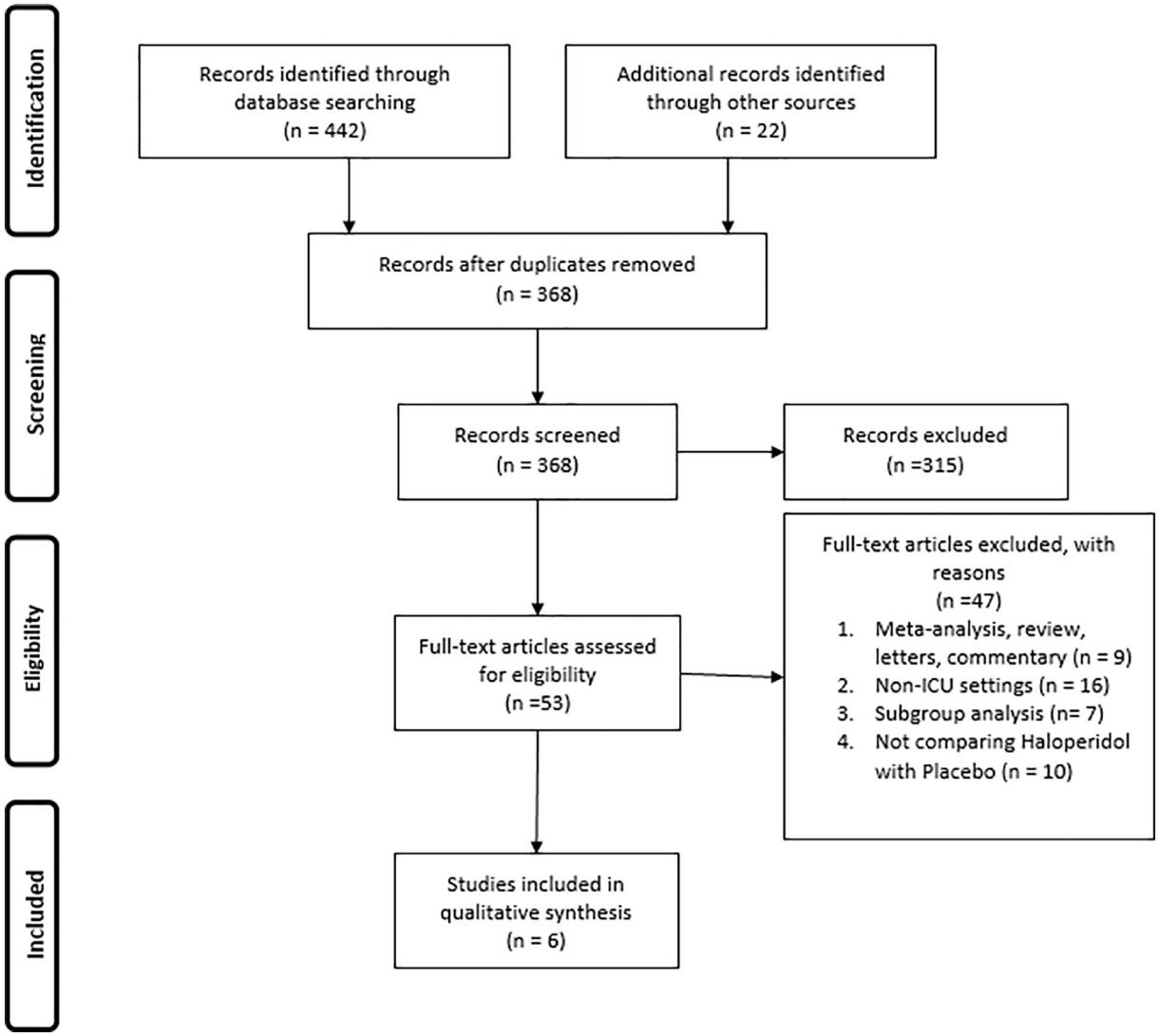

Fig. 1. Flow diagram of literature search and study selection.

2.4. Clinical outcomes

The primary outcome was short-term all-cause mortality, defined as ≤28 days (30-days mortality, ICU mortality or 21-days mortality was used in order of preference if 28-days mortality was not reported). Secondary outcomes included: incidence of delirium defined per either the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC), ICU LOS (days), number of delirium and coma-free days at a longer follow up period, incidence of extrapyramidal symptoms defined by the modified Simpson-Angus Scale, incidence of corrected QT-interval (QTc) prolongation, and serious adverse events as defined by each study.

2.5. Statistical analysis

We calculated the pooled risk ratios (RR) for dichotomous data with their corresponding 95% confidence intervals (CI) using the Mantel-Haenszel method. For continuous data, we calculated the weighted mean difference (MD) with their corresponding 95% CI using the inverse variance test. In studies reported continuous data in median and interquartile range (IQR), we contacted the authors asking about these data in means and standard deviation. In one study, we derived the means and standard deviations values from reported median and/or interquartile ranges using methods described by Wan et al. [18] as we had no response from the author despite several reminders. Random-effects model was used to account for heterogeneity between the included studies. We assessed for heterogeneity using Cochrane Q and I^2 tests. Sensitivity analysis was performed by sequential removal of trials. Subgroup analysis for the primary outcome (short-term mortality) was conducted for the studies that administered haloperidol as a prophylaxis vs treatment of delirium. Meta-regression analysis based on study-level covariates (mean age, daily haloperidol dose, and the Acute Physiology and Chronic Health Evaluation [APACHE] II score) was performed. We used Revman v5.3 windows and Comprehensive Meta-Analysis v3 software for analysis.

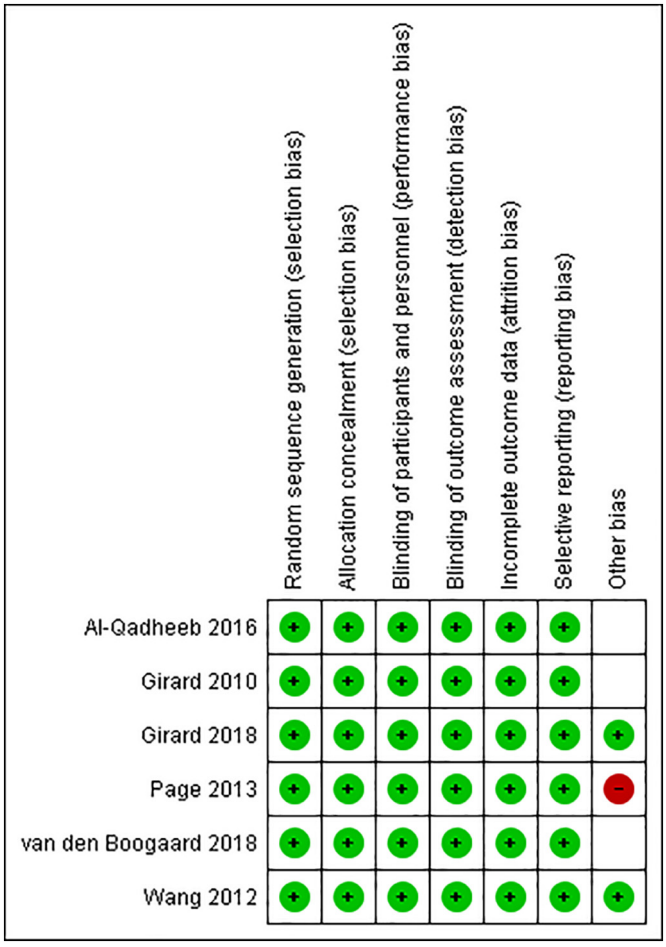

Fig. 2. Risk of bias assessment for each of the included RCTs based on author judgment.

3. Results

3.1. Summary of the included studies

Electronic database search yielded 464 studies. After review, 6 RCTs met our inclusion criteria and were included in the final analysis [19-24]. The search and study selection processes are shown in Fig. 1. All the included studies are of high quality (Fig. 2). Of note, in van den Boogaard et al. study, only haloperidol 2 mg group versus placebo were included since haloperidol 1 mg group was discontinued early during the study, and haloperidol dose of 2 mg was compared to placebo in the primary analyses [23]. Furthermore, Hope-ICU trial by Page et al. has included patients with and without delirium [21]. The total number of patients included in final analysis was 2552 patients (1293 patients in haloperidol group and 1259 patients in the placebo group). Table 1 summarizes the included studies. The mean age 66.59 ± 13.18, 57.8% were males. Acute physiology and chronic health evaluation II (APATCHE II) score ranged between 8.55 and 30. The baseline clinical and demographic characteristics of the included patients are explained in Table 2.

3.2. Clinical outcomes

3.2.1. Primary outcome

There was no significant difference in the short-term all-cause mortality between both groups (RR 0.96; 95% CI 0.81–1.14; P = 0.67; I^2 = 0%) (Fig. 3). Subgroup analysis (prophylactic haloperidol vs treatment) did not show any interaction. Meta-regression analysis did not suggest any covariates effects of the daily haloperidol dose, age, and APACHE II score on the primary outcome. A sensitivity analysis with sequential removal of the trials demonstrated consistent results. Furthermore, we conducted sensitivity analysis by including the 1 mg haloperidol group in the REDUCE trial, and our results remained consistent.

3.2.2. Secondary outcomes

There was no difference in the incidence of delirium (RR 0.93; 95% CI 0.65–1.34; P = 0.70; I^2 = 64%), ICU LOS in days (MD 0.00; 95% CI -0.82-0.83; P = 0.99; I^2 = 0%), or delirium/coma free days (MD 0.09; 95% CI -0.05-0.24; P = 0.21, I^2 = 0%) between both groups (Figs. 4-6). Similarly, meta-regression analysis did not suggest any modifier effects.

Furthermore, haloperidol-treated patients exhibited similar incidence of serious adverse events (RR 0.65; 95% CI 0.23–1.88; P = 0.43; I^2 = 0%), QTc prolongation (RR 0.87; 95% CI 0.63–1.19; P = 0.38; I^2 = 0%), and extrapyramidal symptoms (RR 0.84; 95% CI 0.57–0.1.23; P = 0.37; I^2 = 0%) when compared with placebo (Fig. 7).

4. Discussion

We performed a meta-analysis of only RCTs evaluating the role of haloperidol in the prevention and/or treatment of ICU associated delirium. Our study revealed that haloperidol does not significantly affect short-term mortality, incidence of delirium, ICU LOS, or delirium/coma-free days in critically ill patients. However, we found that haloperidol use was does not increase the incidence of serious adverse events, extrapyramidal symptoms, or QTc interval prolongation.

van den Boogaard et al. conducted a before-and-after treatment pilot study in which haloperidol was used to prevent delirium in mixed ICU population and found that it was associated with lower incidence of delirium and more delirium-free days when compared to placebo [25].

Table 1
Summary of included studies. ICU: Intensive care unit. Mg: Milligram.

Studies	Study design	Patient number	Follow-up period	Inclusion criteria	Haloperidol dose	Duration of Haloperidol
Girard [19]	Multi-center, randomized, double-blind, placebo-controlled trial.	Total:101 Haloperidol:35 Ziprasidone:30 Placebo:36	21 days	Adult mechanically ventilated medical and surgical ICU patients who had an abnormal level of consciousness or were receiving sedative or analgesic medications	-Haloperidol 5 mg every 6 h	Haloperidol was stopped if patient was delirium free for 48 h, experienced a predefined side effects or at day 14 of study period.
Wang [20]	Prospective, randomized, double-blind, and placebo controlled trial in two centers.	Total:457 Haloperidol:229 Placebo:228	28 days	Patients 65 years or older who were admitted to the ICU after noncardiac surgery	Bolus injection of 0.5 mg haloperidol followed by continuous infusion at a rate 0.1 mg/h haloperidol	12 h
Page [21]	Single center double-blind, placebo-controlled randomized trial	Total:141 Haloperidol:71 Placebo:70	28 days	Critically ill patients (≥18 years) needing mechanical ventilation within 72 h of admission.	Haloperidol 2.5 mg Every 8 h	Medication was discontinued on ICU discharge, once delirium-free and coma free for 2 consecutive days, or after a maximum of 14 days of treatment, whichever came first. Medication was restarted if patient developed delirium.
Al-Qadheeb [22]	Single center randomized, double-blind, placebo-controlled trial.	Total:68 Haloperidol:34 Placebo:34	10 days and until dispo-sition	ICU mechanically ventilated patients with subsyndromal delirium	Haloperidol 1 mg every 6 h	Study medication was stopped when one of the following occurred: delirium, ICU discharge, 10 days of therapy had elapsed, or development of adverse effects necessitating study drug discontinuation.
van den Boogaard [23]	Multi-center randomized, double-blind, placebo-controlled tiral	Total:1789 -Haloperidol 1 mg:350 -Haloperidol 2 mg:732 -Placebo:707	90 days	Patients aged 18 years or older, delirium free, with an anticipated ICU stay of at least 2 days	-Haloperidol 1 mg every 8 h -Haloperidol 2 mg every 8 h	Medication was started within 24 h of admission to the ICU through day 28, until ICU discharge (whichever came first), or until delirium occurred.
Girard [24]	Multi-center randomized, double-blind, placebo-controlled, phase 3 trial	Total: 566 Haloperidol: 192 Ziprasidone: 190 Placebo: 184	90 days	Patients18 years of age or older with delirium who were managed in a medical or surgical ICU	−2.5-10 mg every 12 h for patients <70yers −1.25-5 mg every 12 h for patients >70 years. -Patients received up to 10 mg every 12 h and up to 20 mg every 24 h.	Trial drug or placebo was discontinued if patient had no delirium for 48 h, development of a pre-defined side effects, after the 14-days intervention period or at ICU discharge, whichever occurred first.

However, given the observation design of their study and unmeasured confounders, inference is difficult to establish. Unfortunately, van den Boogaard and his colleagues found different results in the REDUCE (pRophylactic halopEriDol Use for Delirium in iCu patiEnts With a High Risk for Delirium) trial, which included >1700 patients [23]. In addition, there was no significant difference in mortality, number of days free of delirium and coma, and other clinical outcomes in MIND-USA (Modifying the Impact of ICU-Associated Neurological Dysfunction-USA) trial which investigated the role of haloperidol in treatment of ICU related delirium [24]. Furthermore, in the Hope-ICU randomized clinical trial, there was no difference between placebo and haloperidol groups in terms of delirium-free days [21]. Our analysis showed no efficacy benefits of haloperidol on all of the studied clinical outcomes —namely, the incidence of delirium, ICU length of stay, and number of delirium or coma-free days during ICU stay.

Despite the increased mortality and morbidity associated with delirium among critically ill patients, optimal pharmacological management of this common condition remains unknown. Though many hypotheses

Table 2
Baseline characteristics of included study population.

Studies	Group	Age in years	Male sex %	APACHE 2 score	Mechani-cally ventilated	Admission type	
						Medical	Surgical
Girard [19]	Haloperidol	51 (35–59)	57%	26 (21−31)	100%	57%	23%
	Placebo	56 (43–68)	61%	26 (21−32)	100%	64%	22%
Wang [20]	Haloperidol	74(5.8)	63.3%	8.70 (3.00)	NA	0	100%
	Placebo	74.4 (7.0)	62.7%	8.55 (2.79)	NA	0	100%
Page [21]	Haloperidol	67.9 (16.5)	52%	19.8 (6.2)	100%	59%	41%
	Placebo	68.7 (14.9)	64%	19.7 (6.9)	100%	70%	30%
Al-Qadheeb [22]	Haloperidol	61.7 16.9	52.9%	19 (17–23)	100%	67.6%	32.4%
	Placebo	59.3 (14.9)	58.8%	20 (17–24)	100%	73.5%	26.5%
van den Boogaard [23]	Haloperidol	66.7 (12.7)	62.7%	19.2 (6.9)	68%	49.9%	46%
	Placebo	67.0 (12.6)	61.4	19.0 (6.8)	64.6%	50.5%	46.4%
Girard [24]	Haloperidol	61 (51–69)	56%	28.5 (23–34)	93%	NA	NA
	Placebo	59 (52–67)	58%	30 (24–34)	92%	NA	NA

BMI: body mass index, APATCHE: Acute Physiology and Chronic Health Evaluation. NA: not available. Data are presented with mean (standard deviation), median (interquartile range) or percent.

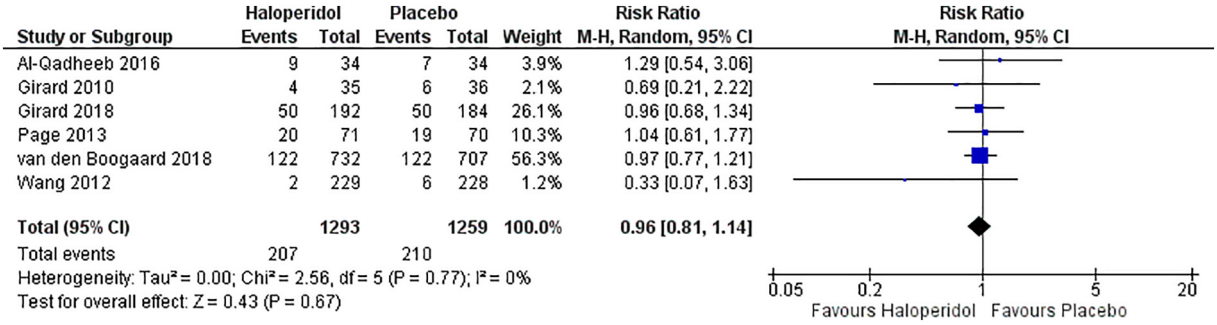

Fig. 3. Forest plot for short-term all-cause mortality.

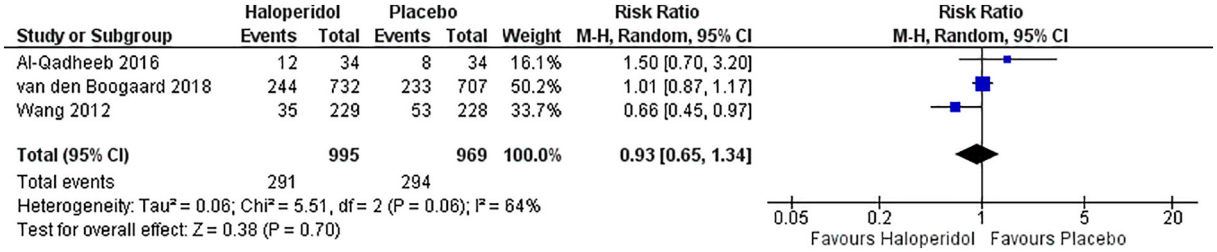

Fig. 4. Forest plot for incidence of delirium.

have been postulated, the underlying pathogenesis continue to be unproven [4,26,27]. Alterations of neurotransmitters, such as an excess of dopamine and cholinergic deficiency likely represent a central pathology. As such, haloperidol does represent an attractive option for the prevention and treatment, primarily due to their D2 dopamine receptor antagonist effects, acetylcholine disinhibition, and reduction of psychotropic sedatives/analgesics [16]. However, there is no clear evidence for benefit of haloperidol for ICU-related delirium, and the current Society of Critical Care guidelines discourage the use of haloperidol in such patients [28].

In this study, we selected mortality as the primary outcome to ensure an objective assessment for the included RCTs. Previous cohort studies have shown conflicting mortality outcomes regarding the use of haloperidol in critically ill patients [29,30]. Additionally, delirium was associated with an increased risk of mortality in three prospective cohort studies [7-9]. Milbrandt et al. demonstrated in a retrospective cohort study that haloperidol administration in ICU-related delirium was associated with significantly lower mortality [30]. However, in our analysis including only RCTs, we found no survival benefit of haloperidol over placebo. Similarly, in a recent Cochrane systematic review, antipsychotics showed no survival benefits for the treatment of delirium in hospitalized non-ICU patients [31].

In an RCT conducted by Wang et al. for non-cardiac surgery patients, treatment of such patients in the ICU was associated with significantly reduced incidence of delirium in patients treated with haloperidol [20]. The included patients in this study were not critically ill, with an APACHE II score of <9 and median ICU stay was less than one day; furthermore, they have low incidence of delirium in both groups, which explains the discrepancy between their findings and our analysis. A subgroup analysis in the REDUCE trial showed no benefit of haloperidol, even in surgical patients [23]. Findings similar to Wang et al. were obtained in previous studies of post-surgical ICU patients treated with various antipsychotic therapy, and haloperidol showed beneficial effects on the clinical outcomes in these patients [15,32-35]. Further sensitivity analysis based on admission type (surgical vs medical) could not be performed in our analysis since the included studies did not account for this data. These data may suggest a different pathophysiological trigger for delirium based on the baseline risk factors and critical illness itself and, thus, differential responses to anti-psychotics [36,37]. These findings highlight the importance of larger RCTs to examine the role of haloperidol in surgical patients admitted to ICU.

Of note, we found no increased safety profile among the treated patients in terms of serious adverse events, prolonged QTc interval or incidence of extrapyramidal symptoms. Although the rates of extrapyramidal symptoms and QTc prolongation were varied among the included studies, it may be a result of various doses and routes of haloperidol administration.

In light of these data, clinicians should focus on non-pharmacological interventions and strategies such as early mobilization and the adoption of mild sedation. Additionally, clinicians should optimize modifiable risk factors and practice using minimal antipsychotics in the event of delirium development.

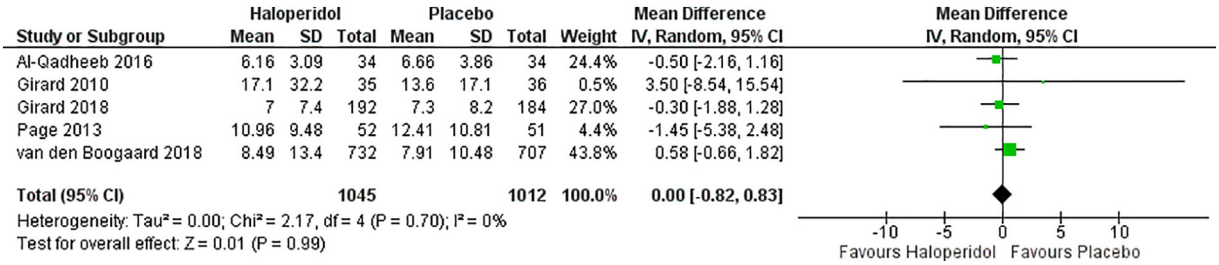

Fig. 5. Forest plot for intensive care unit length of stay.

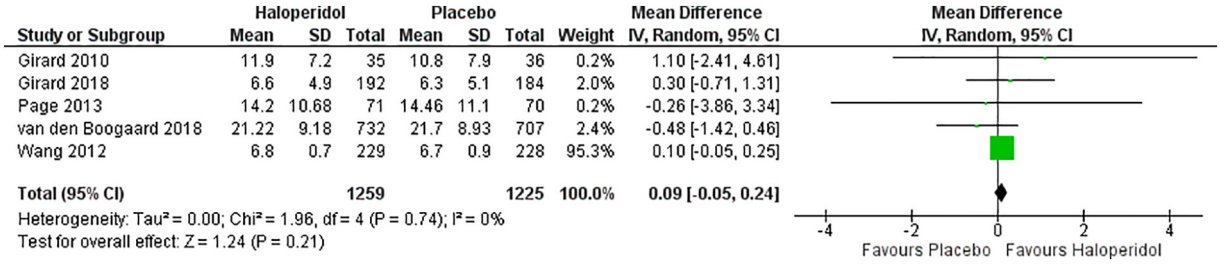

Fig. 6. Forest plot for number of delirium/coma free days.

4.1. Limitations

Our analysis has several pertinent limitations. First, the included studies utilized different doses, routes, and duration of haloperidol. Additionally, each study had different indications regarding discontinuation or resumption of the study medications. Second, the included trials studied different populations, with different risks and severity of illnesses. Third, agitated patients in both groups received open-label antipsychotics, and it is possible that such intervention altered the outcomes, thus, it would need to be controlled in future studies. Fourth, as we lacked patient-level data, we were not able to quantify the effect of sedatives on the clinical outcomes. The use of some sedatives, such as dexmedetomidine, as well as light sedations may have added an additional layer of delirium prevention, while benzodiazepines may have reduced the threshold for delirium. Fifth, we were not able to quantify the effect of various non-pharmacological strategies among the included trials. Several trials have adopted multiple strategies in both arms and controlling such strategies might provide additional insight towards the role of haloperidol vs placebo solely. Sixth, the data for continuous variables were reported by median and IQR which were used to calculate the mean and standard deviation in one study, although we contacted the authors asking about the original data in means but unfortunately, we had no response despite several reminders.

5. Conclusion

In patients admitted to ICU, the use of haloperidol for the management of delirium (prophylaxis or treatment) has no significant reduction of short-term mortality, incidence of delirium, ICU LOS, increased delirium or coma-free days compared with placebo. However,

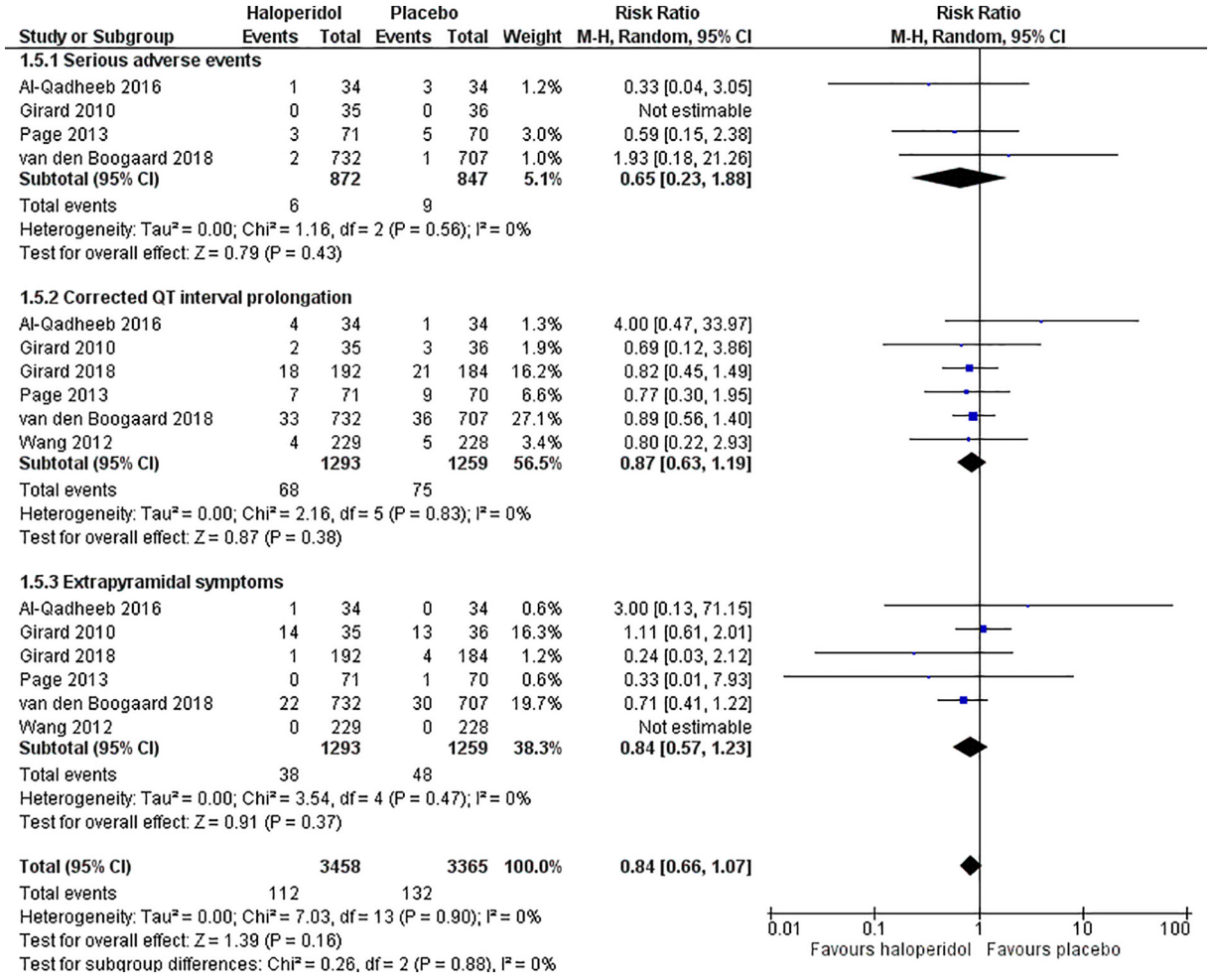

Fig. 7. Forest plot for adverse events.

haloperidol treated patients have no increased risks for development of serious adverse events, QTc prolongation, or extrapyramidal symptoms.

Declaration of interest

No financial support was received for this work and the authors have no conflicts of interest to declare.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. . 5th edArlington, VA: APA; 2013.
[2] van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet (London, England) 2010;375:773–5. https://doi.org/10.1016/S0140-6736(09)61158-2.
[3] Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol A Biol Sci Med Sci 1999;54:B239–46.
[4] Maldonado JR. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. Crit Care Clin 2008;24:789–856. https://doi.org/10.1016/j.ccc.2008.06.004.
[5] Rood P, Huisman-de Waal G, Vermeulen H, Schoonhoven L, Pickkers P, van den Boogaard M. Effect of organisational factors on the variation in incidence of delirium in intensive care unit patients: a systematic review and meta-regression analysis. Aust Crit Care 2018;31:180–7. https://doi.org/10.1016/j.aucc.2018.02.002.
[6] Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27:1892–900. https://doi.org/10.1007/s00134-001-1132-2.
[7] Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753–62. https://doi.org/10.1001/jama.291.14.1753.
[8] Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009;180:1092–7. https://doi.org/10.1164/rccm.200904-0537OC.
[9] Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010;38:2311–8. https://doi.org/10.1097/CCM.0b013e3181f85759.
[10] Vasilevskis EE, Chandrasekhar R, Holtze CH, Graves J, Speroff T, Girard TD, et al. The cost of ICU Delirium and Coma in the Intensive Care Unit Patient. Med Care 2018;56:890–7. https://doi.org/10.1097/MLR.0000000000000975.
[11] Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med 2010;38:1513–20. https://doi.org/10.1097/CCM.0b013e3181e47be1.
[12] Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306–16. https://doi.org/10.1056/NEJMoa1301372.
[13] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and sleep Disruption in Adult patients in the ICU. Crit Care Med 2018;46:e825–73. https://doi.org/10.1097/CCM.0000000000003299.
[14] Moots RJ, Al-Saffar Z, Hutchinson D, Golding SP, Young SP, Bacon PA, et al. Old drug, new tricks: haloperidol inhibits secretion of proinflammatory cytokines. Ann Rheum Dis 1999;58:585–7.
[15] Kalisvaart KJ, de Jonghe JFM, Bogaards MJ, Vreeswijk R, Egberts TCG, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005;53:1658–66. https://doi.org/10.1111/j.1532-5415.2005.53503.x.
[16] Etezadi F, Najafi A, Yarandi KK, Moharari RS, Khajavi MR. ICU sedation with haloperidol-propofol infusion versus midazolam-propofol infusion after coronary artery bypass graft surgery: a prospective, double-blind randomized study. Ann Card Anaesth nd;15:185–9. doi:https://doi.org/10.4103/0971-9784.97974.
[17] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1). https://doi.org/10.1186/2046-4053-4-1.
[18] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135. https://doi.org/10.1186/1471-2288-14-135.
[19] Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 2010;38:428–37.
[20] Wang W, Li H-L, Wang D-X, Zhu X, Li S-L, Yao G-Q, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. Crit Care Med 2012;40:731–9. https://doi.org/10.1097/CCM.0b013e3182376e4f.
[21] Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2013;1:515–23. https://doi.org/10.1016/S2213-2600(13)70166-8.
[22] Al-Qadheeb NS, Skrobik Y, Schumaker G, Pacheco MN, Roberts RJ, Ruthazer RR, et al. Preventing ICU Subsyndromal Delirium Conversion to Delirium with Low-Dose IV Haloperidol: a Double-blind, Placebo-Controlled pilot Study. Crit Care Med 2016;44:583–91. https://doi.org/10.1097/CCM.0000000000001411.
[23] van den Boogaard M, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, et al. Effect of Haloperidol on Survival among Critically Ill adults with a High risk of Delirium: the REDUCE Randomized Clinical Trial. JAMA 2018;319:680–90. https://doi.org/10.1001/jama.2018.0160.
[24] Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and Ziprasidone for Treatment of Delirium in critical Illness. N Engl J Med 2018. https://doi.org/10.1056/NEJMoa1808217.
[25] van den Boogaard M, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Crit Care 2013;17:R9. https://doi.org/10.1186/cc11933.
[26] Hall RJ, Watne LO, Cunningham E, Zetterberg H, Shenkin SD, Wyller TB, et al. CSF biomarkers in delirium: a systematic review. Int J Geriatr Psychiatry 2018;33:1479–500. https://doi.org/10.1002/gps.4720.
[27] Maldonado JR. Delirium pathophysiology: an updated hypothesis of the etiology of acute brain failure. Int J Geriatr Psychiatry 2018;33:1428–57. https://doi.org/10.1002/gps.4823.
[28] Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263–306. https://doi.org/10.1097/CCM.0b013e3182783b72.
[29] Collet MO, Caballero J, Sonneville R, Bozza FA, Nydahl P, Schandl A, et al. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU inception cohort study. Intensive Care Med 2018;44:1081–9. https://doi.org/10.1007/s00134-018-5204-y.
[30] Milbrandt EB, Kersten A, Kong L, Weissfeld LA, Clermont G, Fink MP, et al. Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med 2005;33(226–9) [discussion 263-5].
[31] Burry L, Mehta S, Perreault MM, Luxenberg JS, Siddiqi N, Hutton B, et al. Antipsychotics for treatment of delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev 2018;6:CD005594. https://doi.org/10.1002/14651858.CD005594.pub3.
[32] Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics n.d.;54:124–31. doi:https://doi.org/10.1016/j.psym.2012.12.004.
[33] Mu JL, Lee A, Joynt GM. Pharmacologic agents for the prevention and treatment of delirium in patients undergoing cardiac surgery: systematic review and metaanalysis. Crit Care Med 2015;43:194–204. https://doi.org/10.1097/CCM.0000000000000673.
[34] Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care 2007;35:714–9.
[35] Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. Anesthesiology 2012;116:987–97. https://doi.org/10.1097/ALN.0b013e31825153cc.
[36] Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. J Card Surg 2012;27:481–92. https://doi.org/10.1111/j.1540-8191.2012.01472.x.
[37] Zaal IJ, Devlin JW, Peelen LM, Slooter AJC. A systematic review of risk factors for delirium in the ICU. Crit Care Med 2015;43:40–7. https://doi.org/10.1097/CCM.0000000000000625.