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Haloperidol for preventing delirium in ICU patients: a systematic review and meta-analysis

A. MARRA[1], M. VARGAS[1], P. BUONANNO[1], C. IACOVAZZO[1], K. KOTFIS[2], G. SERVILLO[1]

[1]Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Naples, Italy
[2]Department of Anesthesiology, Intensive Therapy and Acute Intoxications, Pomeranian Medical University, Szczecin, Poland

Abstract. – OBJECTIVE: Delirium, a common behavioral manifestation of acute brain dysfunction in Intensive Care Unit (ICU), is a significant contributor to mortality and worse long-term outcome. Antipsychotics, especially haloperidol, are commonly administered for the treatment and prevention of delirium in critically ill patients while the evidence for the safety and efficacy of these drugs is still lacking. Therefore, we conducted a systematic review of the benefits of haloperidol for the prevention of delirium in ICU patients.

MATERIALS AND METHODS: We made a systematic review and meta-analysis.

RESULTS: Eight RCTs with 2806 patients were included. The prophylactic use of haloperidol did not reduce the delirium incidence (RR: 0.90, 95% CI: 0.69-1.71), the duration of delirium (MD: -0.33, 95% CI: -1.25-0.588) and the delirium/coma free days (MD: 0.08, 95% CI: -0.06-0.23). We did not find an increase of extrapyramidal effects (RR: 1.86, 95% CI: 0.30-11.39), QTc prolongation (RR: 1.11, 95% CI: 0.79-1.55) and arrhythmias (RR: 1.26, 95% CI: 0.72-2.19). The use of haloperidol did not increase the ICU (MD: 0.77, 95% CI: -0.28-1.83) and hospital length of stay (MD: -0.57, 95% CI: -1.32-0.18). Haloperidol did not increase the sedation level (RR: 1.88, 95% CI: 0.76-4.63) and mortality (RR: 0.97, 95% CI: 0.83-1.18).

CONCLUSIONS: Haloperidol did not reduce the delirium incidence, the delirium duration, the delirium/coma free-days and did not increase the incidence of extrapyramidal effects, arrhythmias, the ICU and hospital length of stays and sedation.

Key Words:
Delirium, Prevention, Antipsychotics, Coma, Sedation, Extrapyramidal effects.

Introduction

Delirium is one of the most common behavioral manifestations of acute brain dysfunction in the Intensive Care Unit (ICU). According to the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5), delirium is defined as: (1) a disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention; (2) a change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia; (3) that develops over a short period, hours to days, and fluctuates over time; (4) with evidence from history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one[1]. Delirium occurs in up to 60% to 80% of mechanically ventilated medical and surgical ICU patients and 50% to 70% of non-ventilated medical ICU patients[2-6]. It should be considered as a significant, serious problem and treated as a contributor to mortality, increased length of mechanical ventilation, longer ICU stays, increased cost, and prolonged neuropsychological dysfunction[7-12]. Unfortunately, because delirium is usually "quietly" manifested by negative symptoms, it remains unrecognized by the clinician in a majority of the patients experiencing this complication[13].

The average medical ICU patient has 11 or more risk factors for developing delirium. These risk factors can be divided into predisposing baseline (as with underlying characteristics and comorbidities) and hospital-related, or precipitating factors (such as acute illness, its treatment and ICU management)[14]. Although delirium may be a function of patients' specific underlying illness, it may also be due to medical management

 Corresponding Author: Annachiara Marra, MD, Ph.D; e-mail: dottmarraannachiara@gmail.com

issues and thus, may have preventable causes. Of these risk factors, sedative and analgesic medications and sleep deprivation appear to be the leading iatrogenic, and hence, possibly preventable risk factors for delirium.

In delirious patients, a systematic protocolized search for all reversible precipitants is the first line of action and symptomatic treatment should be considered when available and not contraindicated.

Antipsychotics, especially haloperidol, are commonly administered for the treatment of delirium in critically ill patients[15]. However, evidence for the safety and efficacy of antipsychotics in this patient population is lacking; hence, the 2018 PADIS guidelines did not include specific recommendations for using any particular medication for the treatment or the prevention of delirium[16].

At this time, multicomponent nonpharmacologic interventions, including, promoting sleep hygiene to prevent sleep disruption and the use of early and progressive mobilization[17,18] are effective and strongly recommended to reduce the incidence and duration of ICU delirium and to improve functional outcomes and are recommended for delirium prevention[16,19]. Despite the efficacy and cost-effectiveness of multicomponent nonpharmacologic interventions in delirium prevention[20], pharmacologic interventions, including antipsychotic medications, continue to be evaluated for potential benefit in preventing delirium.

Therefore, we conducted a systematic review and a meta-analysis of the benefits of haloperidol for the prevention of delirium in the ICU setting.

Materials and Methods

Data Sources and Search Strategy

We aimed to identify all randomized controlled trials (RCTs) on adult patients admitted to the ICU. The electronic search strategy was applied with standard filters for identification of RCTs. The databases searched were MEDLINE and PubMed (from inception to July 2019). We applied an English language restriction. The search strategy included the following Mesh terms: haloperidol, antipsychotic, critically ill, ICU, intensive care unit, critical illness, delirium, coma, randomized clinical trial.

Study Selection

We included only published full papers. When more than one RCT was available for each topic data were independently extracted from each study by two authors (MV and PB) using a data recording form developed for this purpose.

Interventions

The interventions of interest were the comparisons between haloperidol and placebo.

Outcome

The primary outcome was the incidence of delirium defined per either the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC). The secondary outcomes were: the delirium duration, 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, incidence of arrhythmias, ICU length of stay (LOS), hospital LOS, sedation and mortality.

Data Extraction and Quality Assessment

The initial data selection was performed by screening titles and abstracts by two pairs of independent reviewers (MV and PB; GS and CI). The full-text copy of potentially relevant studies was obtained for detailed evaluation. Data from each study were independently extracted by two pairs of independent reviewers (MV and PB; GS and CI) using a pre-standardized data abstraction form. Data extracted from the studies were independently checked for accuracy by two reviewers (MV and AM). A quality assessment was conducted by two reviewers (CI and AM) with the GRADE approach. The quality evaluation included (1) the use of randomization sequence generation, (2) the reporting of allocation concealment, (3) blinding, (4) reporting incomplete outcome data, and (5) comparability of the groups at the baseline. Quality assessment was reported in the **Supplementary Table I**. We solved any possible disagreement by consensus through consultation with an external reviewer, if needed.

Quantitative Analysis

This meta-analysis was conducted according to PRISMA guidelines. A mixed random effect with the DerSimonian and Laird method was used in this meta-analysis. The results were graphically represented with forest plot graphs. The Relative Risk (RR) and 95% CI for each outcome were separately calculated for each tri-

al with grouped data using the intention-to-treat principle. The choice to use RR was driven by the design of the meta-analysis based on the RCTs. For continuous data, we calculated the weighted mean difference (MD) with their corresponding 95% CI using the inverse variance test. Tau^2 defined the variance between the studies. The difference in estimates of the treatment effect between the treatment and control groups for each hypothesis was tested using a two-sided z test with statistical significance considered at a *p*-value of less than 0.05. The homogeneity assumption was checked by a Q test with a degree of freedom (df) equal to the number of analyzed studies minus 1. The heterogeneity was measured by I, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 was calculated from basic results obtained from a typical meta-analysis as $I^2 = 100\% A \sim (Q - \_df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degree of freedom. A value of 0% indicates no observed heterogeneity, and larger values demonstrate increasing heterogeneity. The analyses were conducted with OpenMetaAnalyst (version 6) and SPSS version 20 (IBM Corp., Armonk, NY, USA). To evaluate potential publication bias, a weighted linear regression was used, with the natural log of the OR as the dependent variable, and the inverse of the total sample size as the independent variable. This is a modified Macaskill's test that gives more balanced type-I error rates in the tail probability areas in comparison to other publication bias tests[21]. To assess the risk of random errors, we carried out trial sequential analysis (TSA), evaluating whether cumulative data were adequately powered to assess outcomes. In this procedure, according to an alpha value set at 5% to determine significance, we established Z-curves for the primary outcome and secondary outcomes. Using the O'Brien-Fleming alpha spending method, we constructed adjusted significance trial sequential monitoring boundaries, with the hypothesis that a new study was successively added to the meta-analysis when significant testing may have been conducted each time. We calculated a diversity-adjusted required information size for each outcome on the basis of above information. Analysis was conducted using TSA version 0.9 beta software (http://www.ctu.dk/tsa).

We evaluated the FI of the RCTs included in this meta-analysis using a two-by-two contingency table and a *p*-value produced by the Fisher exact test. According to the FI, we defined robust RCTs with FI > 0, and not robust RCTs with FI = 0.

Results

Study Selection

A total of 1367 studies were identified, and 48 full-text articles were assessed for eligibility; finally, 8 RCTs with 2806 patients were included in the final analysis (Table I). Figure 1 shows the flow diagram for included studies.

Characteristics of the Included Studies

Four studies included mechanically ventilated patients admitted in medical and surgical ICU[22-25]group H (30 patients. One study[26] was performed in a surgical ICU, another[27] included non-thoracic cardiac surgery patients in ICU.

Quality Assessment

Seven out of eight of the included RCTs had a low risk of bias. **Supplementary Table I** shows the quality assessment for each included study.

Primary Outcome

The prophylactic use of haloperidol did not reduce the delirium incidence (RR: 0.90, 95% CI: 0.69-1.71). Figure 1 shows the forest plot comparing haloperidol with placebo for the delirium incidence. TSA results indicated that the cumulative Z-curve did not enter the futility area (Figure 1). The estimated required information size to cross the futility boundaries was 2509 randomized patients.

Secondary Outcomes

The duration of delirium and the delirium/coma free days were not different comparing haloperidol with placebo (duration of delirium MD: -0.33, 95% CI: -1.25-0.588. Delirium/coma free days MD: 0.08, 95% CI: -0.06-0.23) (Figure 2). We did not find an increase in the frequency of extrapyramidal effects (RR: 1.86, 95% CI: 0.30-11.39), QTc prolongation (RR: 1.11, 95% CI: 0.79-1.55) and arrhythmias (RR: 1.26, 95% CI: 0.72-2.19) by use haloperidol in delirium prophylaxis (Figure 3). The use of haloperidol did not increase the ICU length of stay (MD: 0.77, 95% CI: -0.28-1.83) and hospital length of stay (MD: -0.57, 95% CI: -1.32-0.18) (Figure 4). Haloperidol did not increase the sedation level (RR: 1.88, 95% CI: 0.76-4.63) (Figure 4) and mortality (RR: 0.97,

Table I. Characteristics of included randomized controlled trials.

Authors	Setting	Participants, n	Comparison groups	Max dose of antipsychotics	Mean Age, y	Delirium diagnosis tool	Outcome assessed
Girard et al[24]	Mechanically ventilated patients in medical and surgical ICU	101	Placebo (36) 5 ml (solution) Haloperidol (35) (5 mg as a solution containing 1 mg/mL) Ziprasidone (30) (40 mg as a solution containing 8 mg/mL)	Patients in the haloperidol group received 15.0 [10.8-17.0] mg/day and patients in the ziprasidone group received 113.3 [81.0-140.0] mg/day	56 51 54	CAM-ICU	Delirium- and coma-free days, days, duration of delirium, use of rescue therapy, mortality, hospital LOS, ICU LOS, cardiac effects, neurologic effects
Wang et al[26]	Surgical ICU	457	Placebo Haloperidol		74 74	CAM-ICU	Delirium incidence,delirium- and coma-free days, use of rescue therapy, mortality, hospital LOS, ICU LOS, cardiac effects, neurologic effects
Page et al[25]	Mechanically ventilated patients in ICU	141	Placebo (70) (0·9% saline placebo intravenously every 8 h) Haloperidol (71)	69 68		CAM-ICU	Delirium- and coma-free days, duration of, delirium short-term delirium symptoms, use of rescue therapy, mortality, hospital LOS, ICU LOS, sedation, cardiac effects, neurologic effects
Abdelgalel et al[22]	ICU	90	Dexmedetomidine (30) (0.2-0.7 mcg/kg/h iv infusion) Haloperidol (30) (0.5- 2 mg/h iv infusion) Placebo (30) (2-8 ml/h iv infusion)		51 51 49	CAM-ICU	Delirium incidence, mortality, hospital LOS, ICU LOS, cardiac effects neurologic effects

Continued

Table I *(Contniued)*. Characteristics of included randomized controlled trials.

Authors	Setting	Participants, n	Comparison groups	Max dose of antipsychotics	Mean Age, y	Delirium diagnosis tool	Outcome assessed
Al-Qadheeb et al[23]	Medical and Surgical ICU	68	Placebo (34) (0.2 mlD5W) Haloperidol (34) (1 mg IV every six hours)		59 62	ICDSC	DSM Delirium incidence, duration of delirium, mortality, ICU LOS, sedation, cardiac effects, neurologic effects
Khan et al[27]	Noncardiac thoracic surgery patients in ICU	135	Haloperidol (0.5 mg administered intravenously by bolus injection over 3 minutes) Placebo (identical in route,appearance, and volume)		60 63	CAM-ICU, DRS-R-98	Delirium incidence, delirium severity, duration of delirium, mortality hospital LOS, ICU LOS, cardiac effects, neurologic effects
Van den Boogaard et al[31]	ICU	1789	Placebo (707) (0.9% sodium chloride) Haloperidol, 1 mg (350) Haloperidol, 2 mg (732)		66 67 67	CAM-ICU, ICDSC	Delirium incidence, delirium- and coma-free days, use of physical restraint, mortality, hospital LOS, ICU LOS, cardiac ffects, neurologic effects

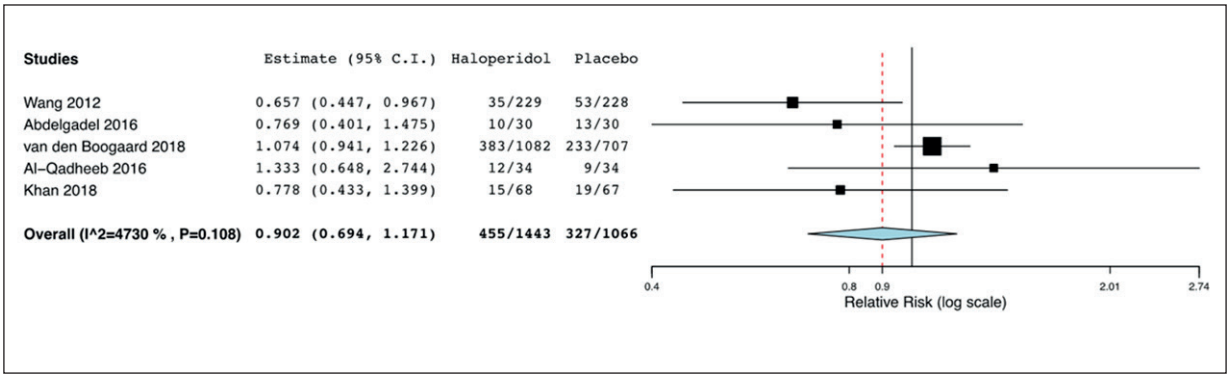

Figure 1. Delirium Incidence.

95% CI: 0.83-1.18) (Figure 5) of treated patients. No included studies had a fi more than zero[28].

Dicussion

In this systematic review evaluating 8 RCTs with 2806 patients we found that haloperidol 1) did not reduce the delirium incidence, the delirum duration, the delirum/coma free-days and 2) did not increase the incidence of extrapyramidal effects, arrythytmias, the ICU and hospital lenght of stays and sedation.

Among medical ICU patients, delirium has been shown to be a strong predictor of increased duration of mechanical ventilation, longer length of ICU stay, higher costs, prolonged neuropsychological dysfunction, and even death[7,9,10,29,30].

Two small studies on delirium prophylaxis with antipsychotics showed that a low dose of haloperidol may reduce the occurrence of delirium in ICU patients[26,31]. Wang et al[26] studied prophylactic haloperidol administration after cardiac surgery and actually found a lower prevalence of postoperative delirium associated with haloperidol, though this study was of a low severity of illness cohort and may not apply to truly critically ill patients with septic shock and ARDS. By contrast, the HOPE ICU randomized controlled trial[25] placebo-controlled randomised trial in a general adult intensive care unit (ICU showed no benefit of haloperidol administration for delirium

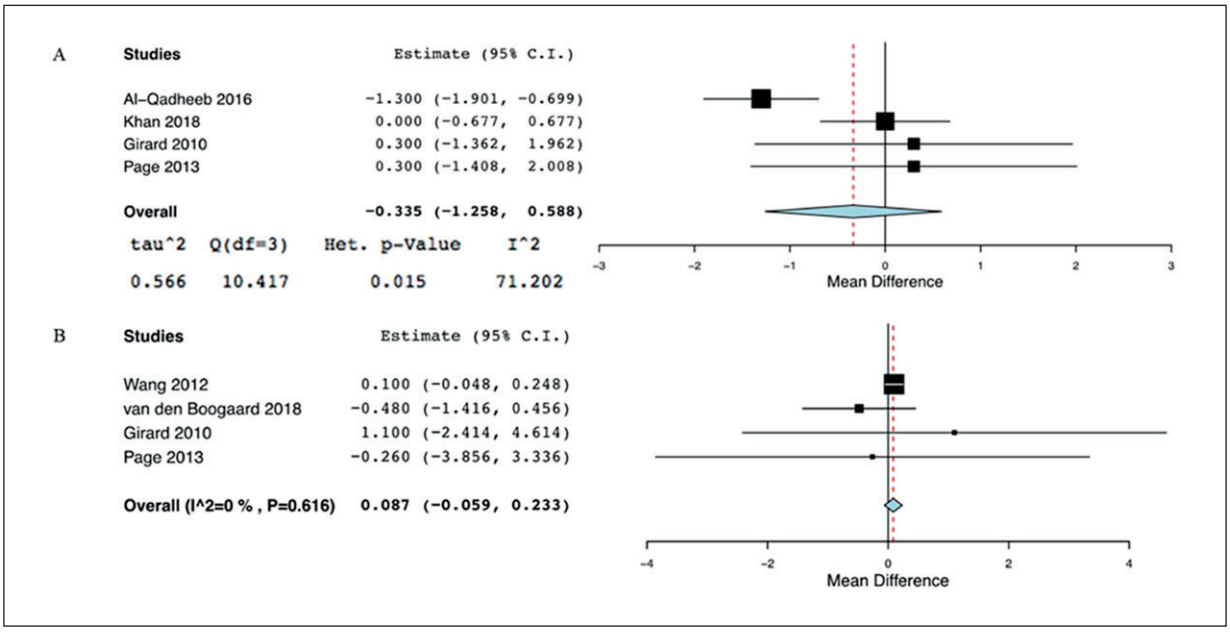

Figure 2. Delirium duration (**A**) and coma free days (**B**).

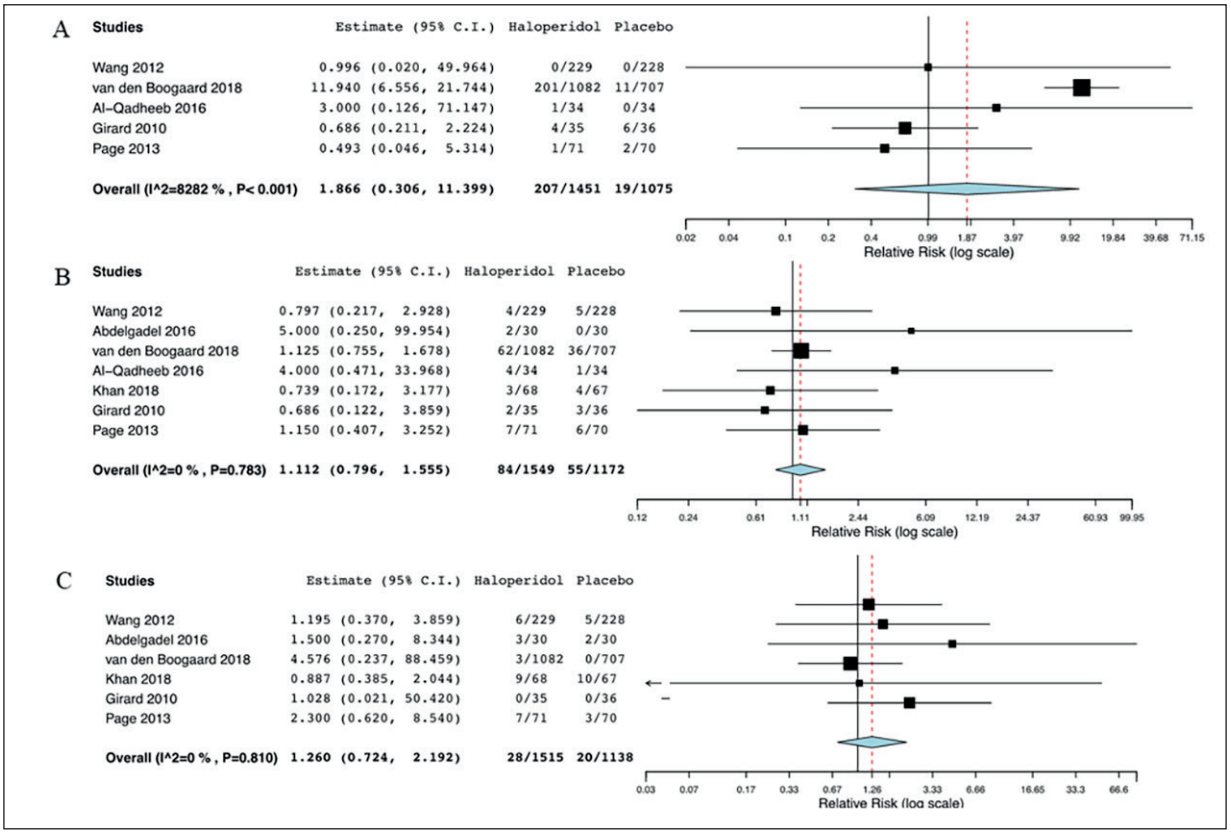

Figure 3. Extrapyramidal effects (**A**), QTc prolongation (**B**) and arrhythmias (**C**).

prophylaxis in a mixed population of medical and surgical adult ICU patients. Similar results were find by Al-Qadheeb et al[23]double-blind, placebo-controlled trial. Setting: Three 10-bed ICUs (two medical and one surgical, that showed that a low-dose scheduled haloperidol, initiated early

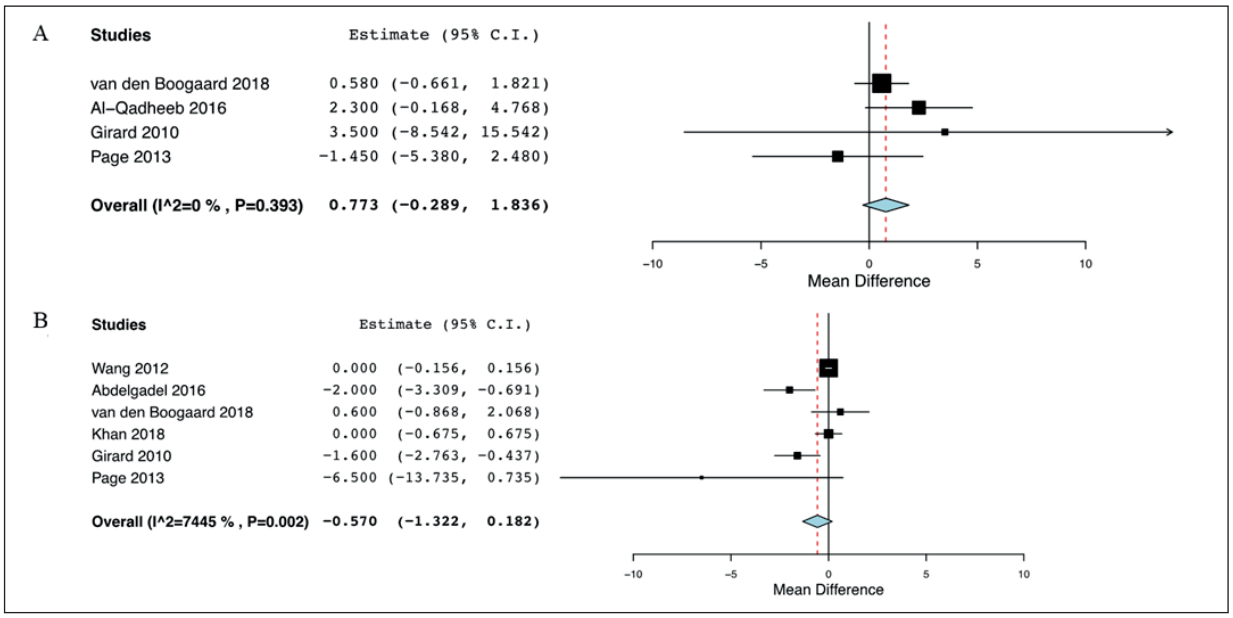

Figure 4. ICU (**A**) and Hospital (**B**) LOS.

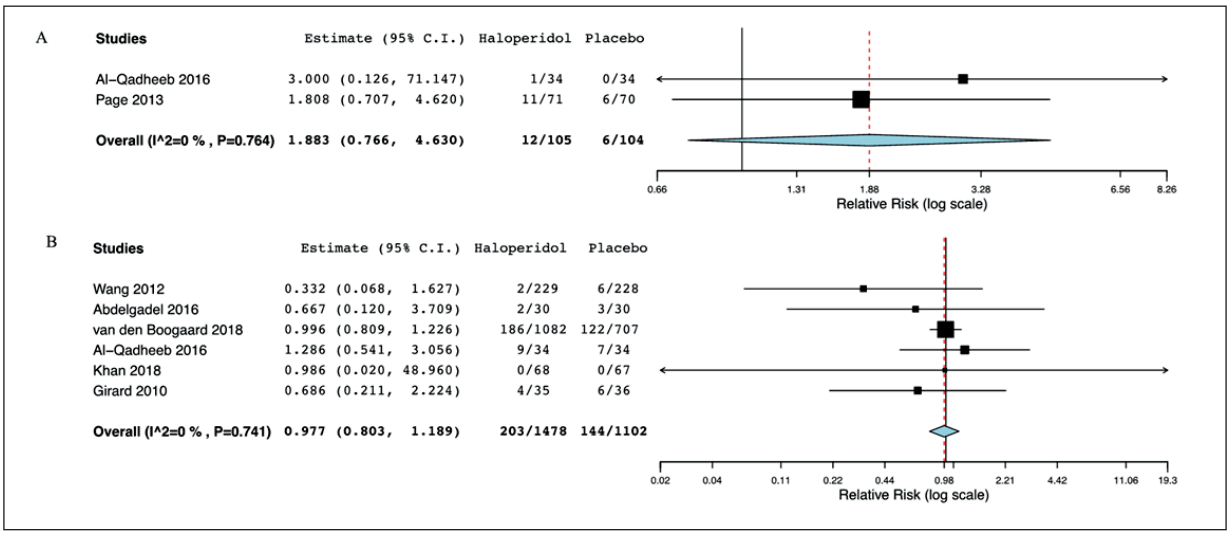

Figure 5. Sedation level (**A**) and mortality (**B**).

in the ICU stay, did not prevent delirium and has little therapeutic advantage in mechanically ventilated, critically ill adults with subsyndromal delirium. Abdelgalel[22] group H (30 patients compared the effects of effects of early prophylactic use of dexmedetomidine or haloperidol on the incidence of delirium during NIV and showed that dexmedetomidine is more effective than haloperidol for prevention of delirium.

Duration of delirium is another important outcome, given its associations with poor clinical outcomes. In our systematic review, compared with placebo, haloperidol did not have an effect on the delirium duration in the overall population. Girard et al[24] conducted a randomized, double-blind, placebo-controlled trial to test the hypothesis that antipsychotics would improve days alive without delirium or coma. They included 101 mechanically ventilated medical and surgical ICU patients and showed that treatment with antipsychotics did not improve the number of days alive without delirium or coma[24]. In another study[23] haloperidol use did not influence the proportion of 12-hour ICU shifts patients' spent alive without coma (SAS $\leq$ 2) or delirium, the time to first delirium occurrence nor delirium duration.

Since delirium is associated with higher mortality[7], it is important to evaluate whether delirium prevention strategies reduce mortality. In our systematic review, haloperidol did not have an effect on mortality.

Hospital LOS is often examined to determine the cost-effectiveness of an intervention, including delirium prevention methods[20]. In our review, there was no effect of haloperidol compared with placebo on ICU and hospital length of stay. We also examined the effect of antipsychotics on sedation and found no statistically significant differences comparing haloperidol with placebo.

Finally, we examined harms of antipsychotics, including the incidence of extrapyramidal effects, and arrythmias and we did not find any significant differences between haloperidol and placebo.

Our findings are consistent with more recent systematic reviews[32,33] that have included some of the more recent studies. These two reviews were conducted in a heterogeneous population while our data were related to critically ill patients. Moreover, Chen et al[33], found that compared with the control group, the use of haloperidol significantly decreased the duration of delirium while our results showed no effect of haloperidol on delirium duration.

In our systematic review there were no evidence that the administration of haloperidol in critically ill patients led to a shorter duration of delirium and coma and at the same time did not increase the incidence of extrapyramidal effects, arrythmias, sedation, survival and lengths of stay in the ICU and hospital. Agitation remains a common motivation for use of haloperidol in critical ill patients and could be a useful agent for the management of agitation despite showing little effect on delirium.

A major strength of this systematic review was the inclusion of data focused on the popu-

lation of critically ill patients in which delirium have a high prevalence and is associated with worse outcome. Therefore, preventive treatment for delirium may be beneficial but the evidence for use of antipsychotics in the ICU is weak and evidence on haloperidol as a prophylactic agent against delirium needs to be carefully analyzed before antipsychotics can be routinely used. Our findings should be interpreted in the context of several limitations. First, the existing data were limited for some of the critical outcomes. Second, there was heterogeneity in dosing, route of administration, and assessment of outcomes.

Conclusions

At this time, we have few data as to which antipsychotic medications are most suitable for delirium prevention. In patients exhibiting delirium, the basic tenets of patient management, such as restoration of sleep/wake cycles, timely removal of catheters, early mobilization, minimization of unnecessary noise/stimuli, and frequent reorientation, should be applied. All of these strategies are summarized and operationalized in the evidence-based ABCDEFs of ICU care (spontaneous Awakening trials, spontaneous Breathing trials, Coordination of care and Choice of sedative, Delirium monitoring and management, Early mobility and Family engagement)[16,34]. Protocols and evidence-based strategies for prevention and treatment of delirium will no doubt emerge as more evidence becomes available from ongoing randomized clinical trials of both nonpharmacologic and pharmacologic strategies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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