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Effects of Haloperidol on Delirium in Adult Patients: A Systematic Review and Meta-Analysis

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Significance of the Study

- This study assessed the effects of haloperidol for prevention and treatment of delirium in adult patients. Haloperidol prophylaxis with a dose of ≥5 mg/day might help reduce the incidence of delirium in surgical patients. Haloperidol exhibited similar effects as the second-generation antipsychotics. However, the current evidence is based on a small patient population, and further studies with larger sample sizes are required.

Keywords
Haloperidol · Delirium · Antipsychotics

Abstract

Objective: The aim of this systematic review and meta-analysis was to investigate whether or not the use of haloperidol could reduce the incidence of delirium in adult patients. ***Subjects and Methods:*** PubMed, Embase, the Cochrane Library, Elsevier, Wiley, and Ovid were searched for randomized controlled trials and prospective interventional cohort studies that compared haloperidol with placebo for delirium prophylaxis or with second generation antipsychotics for delirium treatment. The primary end point was the incidence and severity of delirium. After reviewing 272 relevant articles, 10 studies with 1,861 patients were finally included (haloperidol vs. placebo in 8 studies [*n* = 1,734], and haloperidol vs. second-generation antipsychotics in 2 studies [*n* = 127]). Revman 5.3 was used for the data analysis. ***Results:*** Compared with placebo, a high dose of prophylactic haloperidol (≥5 mg/day) may help reduce the incidence of delirium in surgical patients (risk ratio 0.50, 95% CI 0.32, 0.79). There were no differences in the duration of delirium, QTc interval prolongation, extrapyramidal symptoms, intensive care unit stay, hospital stay, or mortality between the haloperidol and placebo groups. For delirium treatment, haloperidol exhibited similar effects as the second-generation antipsychotics. ***Conclusions:*** In this study, the limited available data revealed that prophylaxis haloperidol at a dose of ≥5 mg/day might help reduce delirium in adult surgical patients. Further outcome studies with larger sample sizes are required to confirm these findings.

Y.S. and K.P. contributed equally to this study.

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Introduction

Delirium is a neuropsychiatric disorder characterized by an acute onset of confusion and alterations of consciousness [1, 2], resulting in increased complications, prolonged hospitalization, and worse outcomes [3–5]. The incidence of delirium ranges from 29 to 64% in medical in-patients [3, 4] and even higher in intensive and palliative care settings [5]. The risk factors include elderly patients, cognitive impairment, prior delirium, abnormal sodium, potassium or glucose, preoperative narcotics, tobacco or psychotropic drug use, apolipoprotein E4 carrier status, and postoperative hypotension [6–11].

Haloperidol, a typical antipsychotic, is still used widely to treat delirium. However, the results from previous studies are inconsistent. Several studies reported that the use of haloperidol was associated with a decrease in delirium incidence [12–15], while others did not report a beneficial effect of haloperidol [16–19]. It was also reported that prophylactic low-dose haloperidol did not reduce the incidence of delirium [20, 21].

Recently, 2 reviews showed promising results on haloperidol for delirium management, but they failed to summarize the evidence by means of a quantitative meta-analysis [22, 23]. Hence, a systematic review and meta-analysis were designed to assess the effects of haloperidol for the prevention and treatment of delirium in adult patients.

Materials and Methods

Literature Search

Two researchers (Y.S. and K.P.) independently performed a comprehensive literature search to identify trials that compared the effects of haloperidol with placebo or antipsychotics on the outcomes of delirium in adult patients. PubMed, Embase, the Cochrane Library, Elsevier, Wiley, and Ovid were searched until May 1, 2017. A basic search was performed using medical subject headings and free text words: "haloperidol," "antipsychotics," and "delirium." No language or publication date restriction was applied. In addition, references and previous reviews were manually checked for other potentially eligible trials. Any disagreement at any stage of this study was resolved by group discussion and consensus.

The inclusion criteria were adult patients, haloperidol prophylaxis or treatment, comparisons of haloperidol with placebo or second-generation antipsychotics, delirium-related outcomes, randomized controlled trials (RCTs), and prospective interventional cohort trials. The search flow diagram is shown in Figure 1. A total of 272 articles relevant to the search terms were identified, and 10 studies were finally included in this study.

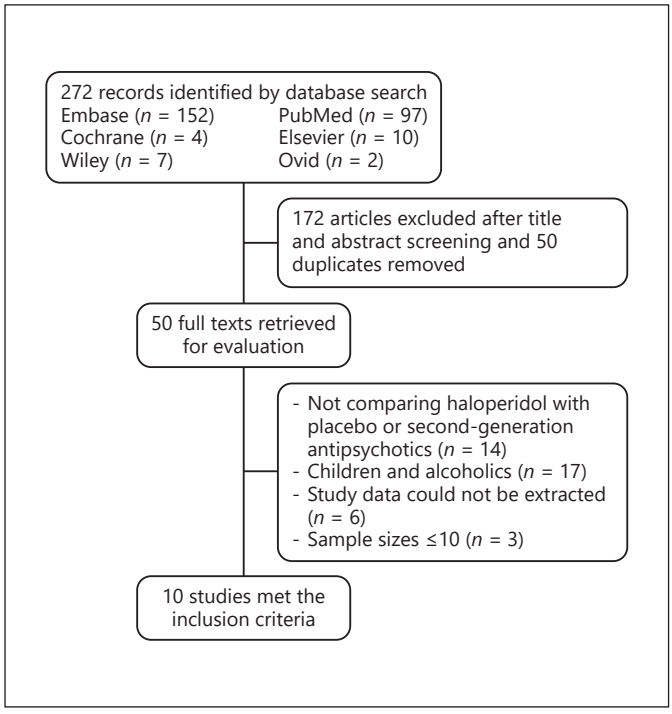

Fig. 1. Flowchart for study inclusion and exclusion.

Data Extraction and Quality Assessment

The following data were independently extracted by 2 reviewers (Y.S. and K.P.): first author, year of publication, study design, inclusion and exclusion criteria, interventions, number of patients, and outcomes. The primary end point was the incidence and severity of delirium. Secondary end points were the duration of delirium, mortality, length of intensive care unit (ICU) stay, length of hospital stay, and the incidence of corrected QT (QTc) interval prolongation and extrapyramidal symptoms. The severity of delirium was measured by revised Delirium Rating Scale (DRS-R98) scores, and Mini-Mental State Examination (MMSE) scores.

The methodological quality of each included study was evaluated using the Cochrane risk of bias assessment tool [24]. Disagreements on data abstraction and quality assessment were resolved by group discussion.

Statistical Analysis

All analyses were performed using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Dichotomous variables, including the incidence of delirium, mortality, QTc interval prolongation, and extrapyramidal symptoms, were reported as the risk ratio (RR) with 95% confidence interval (CI), while mean difference (MD) with 95% CI was used for the continuous variables, including the duration of delirium, ICU stay, hospital stay, DRS-R98 scores, and MMSE scores. The results of risperidone and olanzapine groups were combined using the calculator in Revman [25]. A p value <0.05 was considered statistically significant.

The heterogeneity among studies was assessed using the I^2 test. If the I^2 index was ≤50%, the fixed-effect model was selected to

Table 1. Characteristics of the included studies

Study	Design	Inclusion criteria (setting)	Exclusion criteria	Interventions (patients, *n*)	Outcomes
Al-Qadheeb [16], 2016	RCT, delirium prophylaxis	Mechanically ventilated patients with subsyndromal delirium (ICU)	Age ≥85 years, safety concerns associated with haloperidol, condition might preclude delirium evaluation, admitted to ICU for ≥4 days	Haloperidol (*n* = 34): 1 mg every 6 h until delirium occurred, 10 days of therapy elapsed, or ICU discharge Placebo (*n* = 34): 5% dextrose	Incidence of delirium, delirium-related outcomes, QTc interval prolongation, extrapyramidal symptoms, ICU stay, ICU disposition, hospital disposition
Fukata [17], 2014	Randomized, open-label prospective trial, delirium prophylaxis	Age ≥75 years, scheduled for elective abdominal or orthopedic surgery (surgical)	Emergency surgery, delirium, use of antipsychotics, antidepressants, hypnotics or anti-Parkinson agents within 2 weeks before surgery	Haloperidol (*n* = 59): 2.5 mg daily for 3 days after surgery Placebo (*n* = 60): details not mentioned	NEECHAM scores, postoperative delirium, duration of delirium
Fukata [14], 2017	Randomized, open-label prospective trial, delirium prophylaxis	Age ≥75 years, scheduled for elective abdominal or orthopedic surgery (surgical)	Emergency surgery, delirium, use of antipsychotics, antidepressants, hypnotics or anti-Parkinson agents within 2 weeks before surgery	Haloperidol (*n* = 101): 5 mg daily for 5 days after surgery Placebo (*n* = 100): details not mentioned	NEECHAM scores, postoperative delirium, duration of delirium
Grover [27], 2011	RCT, delirium treatment	Age >18 years, diagnosis of delirium (not mentioned)	Alcohol or benzodiazepine withdrawal, dementia, terminal illness, comorbid psychotic or mood disorders	Haloperidol (*n* = 21): 0.25–5 mg/day Risperidone (*n* = 20): 0.5–2 mg/day Olanzapine (*n* = 23): 1.25–10 mg/day	DRS-R98 scores, MMSE scores, side effects
Grover [25], 2016	RCT, delirium treatment	Age >18 years, diagnosis of delirium (not mentioned)	Alcohol or benzodiazepine withdrawal, dementia, terminal illness, comorbid psychotic or mood disorders	Haloperidol (*n* = 32): 0.25–1.25 mg/day Quetiapine (*n* = 31): 12.5–75 mg/day	DRS-R98 scores, MMSE scores, side effects
Kalisvaart [12], 2005	RCT, delirium prophylaxis	Age ≥70 years, scheduled for hip surgery (surgical)	Delirium, haloperidol allergy, use of cholinesterase inhibitors, Parkinson, epilepsy, or levodopa treatment, inability to participate in interviews, delay of surgery, QTc prolongation	Haloperidol (*n* = 212): 1.5 mg/day for 3 days after surgery Placebo (*n* = 218): identical in appearance	Incidence of delirium, DRS-R98 score, duration of delirium, hospital stay
Kaneko [13], 1999	RCT, delirium prophylaxis	Scheduled for elective gastrointestinal surgery (surgical)	Not mentioned	Haloperidol (*n* = 38): 5 mg for 5 days after surgery Placebo (*n* = 40): normal saline	Incidence of delirium, use of pain medication, sleep pattern
Page [19], 2013	RCT, delirium prophylaxis	Age ≥18 years, needing mechanical ventilation within 72 h of admission (ICU)	Allergy to haloperidol, moderate to severe dementia, Parkinson disease, structural brain damage, chronic antipsychotic use	Haloperidol (*n* = 71): 2.5 mg every 8 h, irrespective of coma or delirium status Placebo (*n* = 70): 0.9% saline	Delirium-free and coma-free days in first 14 days after randomization, delirium-free and coma-free days to day 28, ventilator-free days to day 28, mortality at 28 days, length of critical care, hospital stay, adverse effects
Schrøder Pedersen [18], 2013	Prospective interventional cohort study, delirium prophylaxis	Age ≥18 years, scheduled for open cardiac surgery with cardiopulmonary bypass (surgical)	Death or transfer to another department within 24 h after surgery, coma or heavy sedation throughout the admission	Haloperidol (*n* = 123): 2.5–5 mg orally, 3 times a day for 1.5 days, then tapered over 2 days Placebo (*n* = 117): details not mentioned	Incidence, onset, and duration of postcardiotomy delirium, proportion of delirium- and coma-free days, length of stay, all-cause complications, 180-day mortality
Wang [15], 2012	RCT, delirium prophylaxis	Age ≥70 years, admitted to ICU after noncardiac surgery (surgical and ICU)	History of schizophrenia, epilepsy, parkinsonism, use of cholinesterase inhibitor or levodopa treatment, inability to communicate	Haloperidol (*n* = 229): 0.5 mg followed by continuous infusion of 0.1 mg/h for 12 h Placebo (*n* = 228): normal saline	Incidence of delirium during the first 7 days after surgery, safety and tolerability of haloperidol, time to delirium onset, daily prevalence of delirium, number of delirium-free days, ICU stay, adverse effects, 28-day mortality

RCT, randomized controlled trial; ICU, intensive care unit; DRS-R98, Delirium Rating Scale-Revised 98; NEECHAM, Neelon and Champagne Confusion Scale; MMSE, Mini-Mental State Examination.

Table 2. Risk of bias in the included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Al-Qadheeb [16], 2016	Low risk	Low risk	low risk	Low risk	Low risk	Low risk	Low risk
Fukata [17], 2014	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Fukata [14], 2017	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Grover [27], 2011	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Grover [25], 2016	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kalisvaart [12], 2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kaneko [13], 1999	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Page [19], 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schrøder Pedersen [18], 2013	High risk	High risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Wang [15], 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

calculate the pooled effects; otherwise, a random-effect model was used [24, 26]. The following sensitivity analyses were performed to test the robustness of the results: (a) whether the quality of publication (RCT or non-RCT) could influence the results, and (b) subgroup analyses according to the data of surgical versus ICU settings and high doses (≥5 mg) versus low doses (<5 mg) of haloperidol.

Results

Study Selection and Characteristics

The study characteristics are described in Table 1. The patient populations ranged from 63 to 457. Seven studies were RCTs, 2 were randomized, open-label prospective trials, and 1 was a prospective interventional cohort study [12–19, 25, 27]. A risk assessment of the included studies is presented in Table 2.

Haloperidol versus Placebo for Delirium Prophylaxis

Eight studies [12–19] compared haloperidol with placebo for preventing delirium in surgical and ICU patients. Overall, haloperidol prophylaxis did not decrease the incidence of delirium compared with placebo (RR 0.84, 95% CI 0.62, 1.13, $p = 0.24$, $I^2 = 55\%$; Fig. 2) [12–18]. Subgroup analysis based on surgical versus ICU patients did not detected any significance with $I^2 = 58.6\%$ (Fig. 2a). Subgroup analysis based on haloperidol doses showed that the use of a high dose of haloperidol (≥5 mg/day) may reduce the incidence of delirium (RR 0.50, 95% CI 0.32, 0.79, $p = 0.003$, $I^2 = 0\%$; Fig. 2b). Of the 8 studies, 5 [12, 16–19] showed that haloperidol prophylaxis did not shorten the duration of delirium (MD –0.75 days, 95% CI –1.97, 0.46, $p = 0.22$, $I^2 = 84\%$; Fig. 3a).

In the sensitivity analyses, the I^2 index values in the outcome of delirium incidence remained above 30%. Substantial heterogeneity of $I^2 = 57\%$ was found when we included only RCTs. For the outcome of duration of delirium, substantial heterogeneity still existed ($I^2 = 86\%$) when only RCTs were included.

Regarding the side effects associated with haloperidol, 3 studies [11, 15, 16] showed that there were no differences in QTc interval prolongation or the incidence of extrapyramidal symptoms (Fig. 3b, c). In addition, there were no differences in ICU stay, hospital stay, or mortality between the haloperidol and placebo groups (Fig. 4).

Haloperidol versus Second-Generation Antipsychotics for Delirium Treatment

For delirium treatment, no difference was found in DRS-R98 or MMSE scores at 0, 3, and 6 days between the haloperidol and second-generation antipsychotics treatment groups (Fig. 5, 6) [24, 26].

Discussion

This systematic review and meta-analysis suggests that a high dose (≥5 mg/day) of haloperidol prophylaxis might help reduce delirium in surgical patients. However, use of haloperidol did not influence the duration of delirium, QTc interval prolongation, extrapyramidal symptoms, ICU stay, hospital stay, or mortality. For delirium

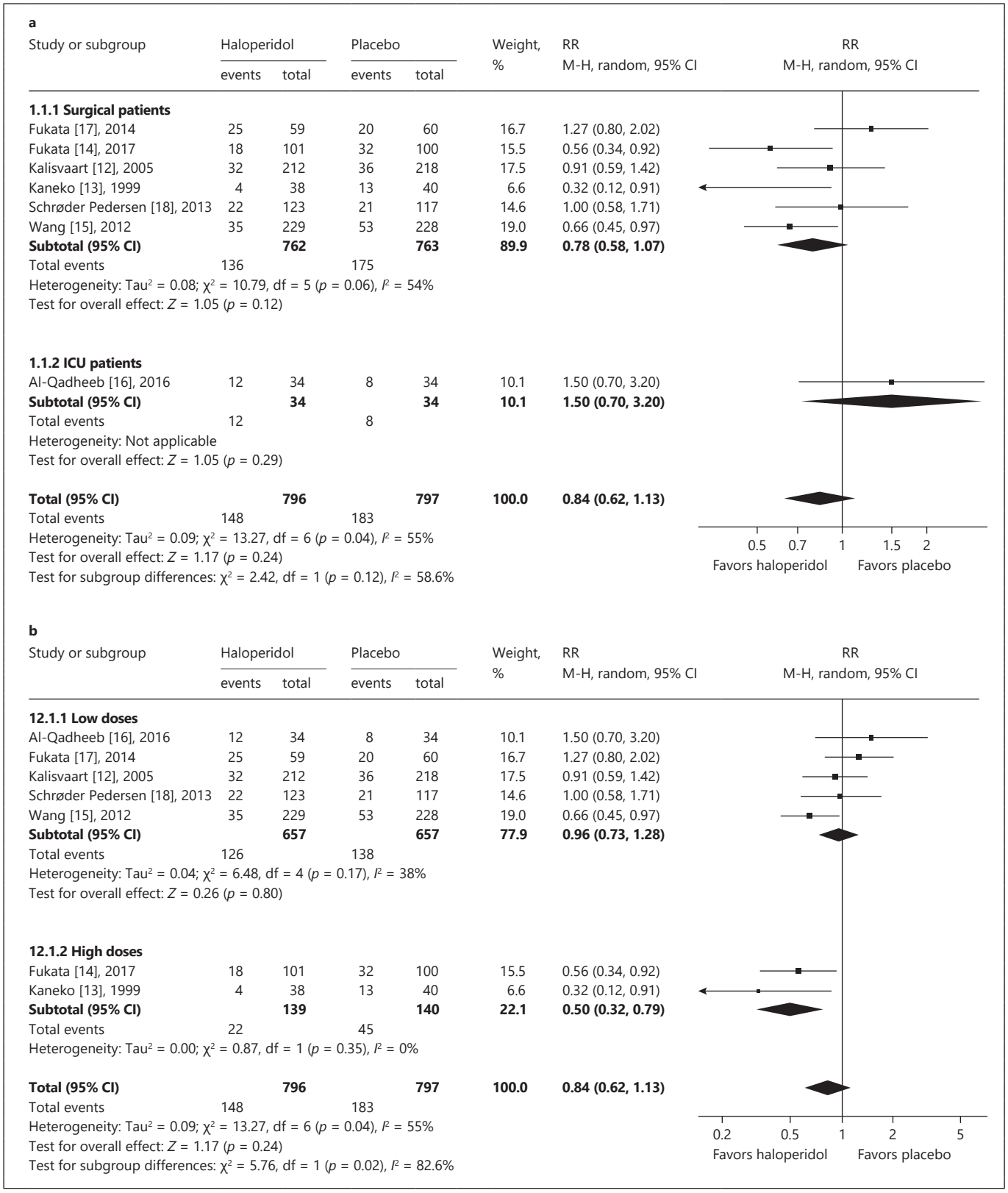

Fig. 2. Meta-analysis of haloperidol versus placebo for the incidence of delirium: surgical patients versus ICU patients (**a**), low versus high dose (**b**).

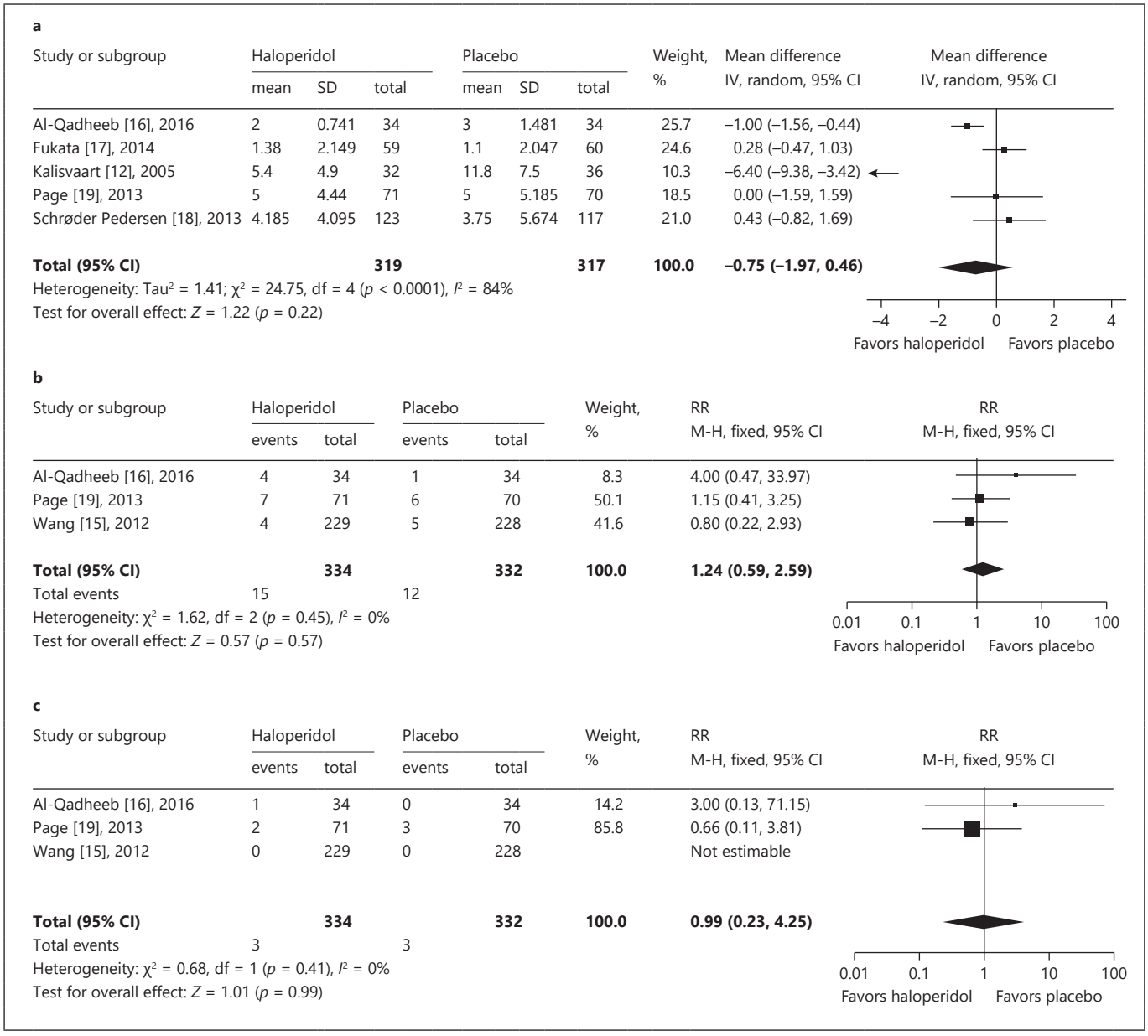

Fig. 3. Meta-analysis of haloperidol versus placebo for duration of delirium (**a**), QTc interval prolongation (**b**), and extrapyramidal symptoms (**c**).

treatment, haloperidol had similar therapeutic effects on MMSE and DRS-R98 scores as the second-generation antipsychotics.

Subgroup analysis showed that a high dose of haloperidol (≥5 mg/day) reduced the incidence of delirium in surgical patients. However, more evidence is needed due to the limited number of studies included for this outcome. Kalisvaart et al. [12] used a small dose of haloperidol (1.5 mg/day) and found no difference in delirium outcomes between the groups. Wang et al. [15] also used a small dose (0.5 mg intravenous bolus injection followed by continuous infusion of 0.1 mg/h for 12 h) and reported a lower incidence of delirium in the haloperidol group, suggesting that continuous infusion may be a better

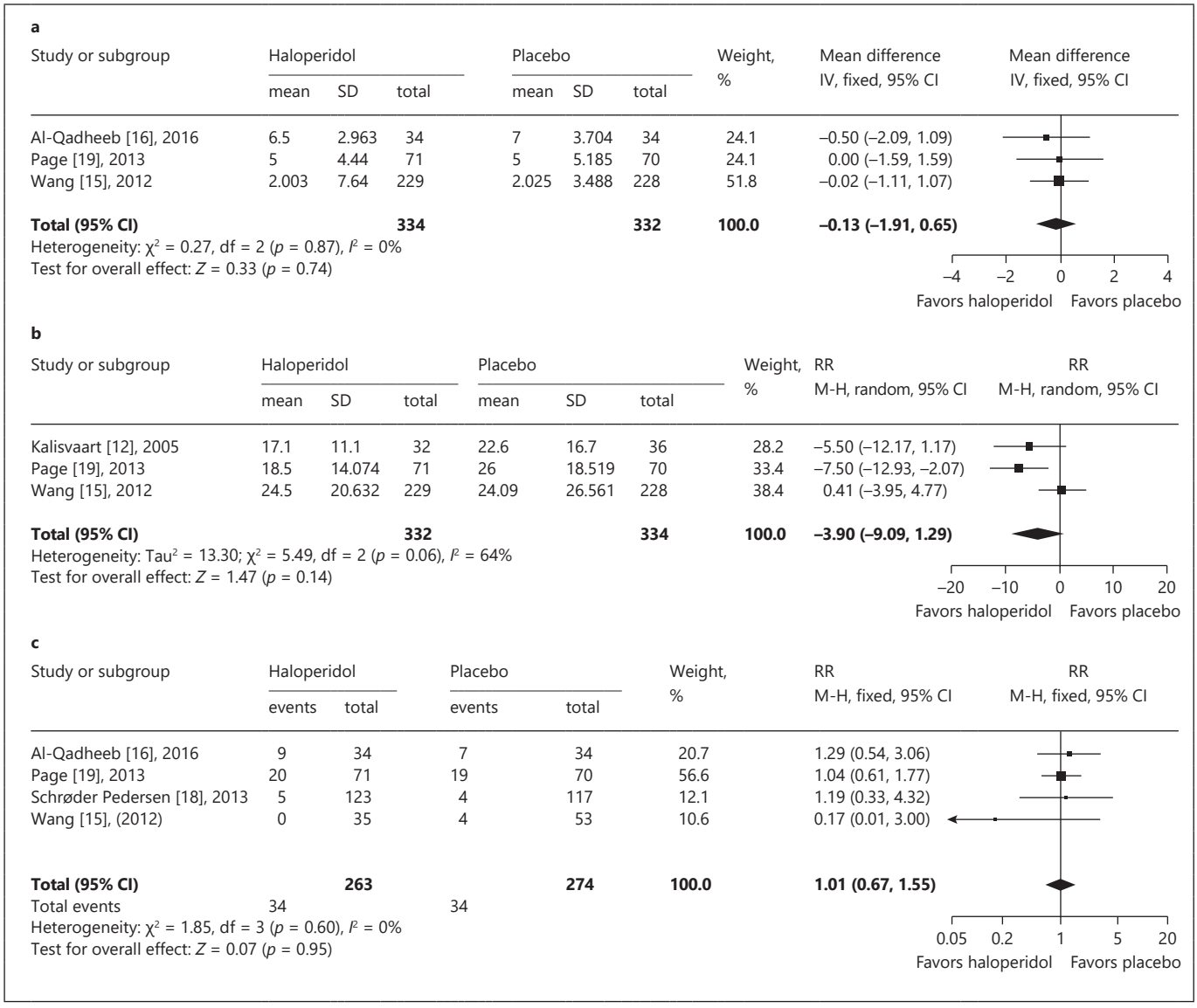

Fig. 4. Meta-analysis of haloperidol versus placebo for ICU stay (**a**), hospital stay (**b**), and mortality (**c**).

choice. Besides, initiating the therapeutic intervention as early as possible by detecting the early signs of delirium is essential for preventing its aggravation. With regard to the early stage of postoperative delirium, a concept exists called "subsyndromal delirium" [28–31], which is a frequent and clinically important condition that falls on a continuum between no symptoms and full delirium. The importance of starting the prophylactic intervention during the subsyndromal stage has also been reported. Hakim et al. [32] showed that early treatment with risperidone during the subsyndromal phase had a preventative effect against postoperative delirium after on-pump cardiac surgery in the elderly.

A higher dose of haloperidol may cause a higher incidence of side effects. In the study by Page et al. [19] the incidences of QTc interval prolongation and extrapyramidal symptoms in the haloperidol group were 9.86 and 2.82%, respectively, compared to 1.75 and 0% in the study by Wang et al. [15] with a low dose of 1.7 mg/day. Currently, a dose of 3–5 mg/day of haloperidol is suggested,

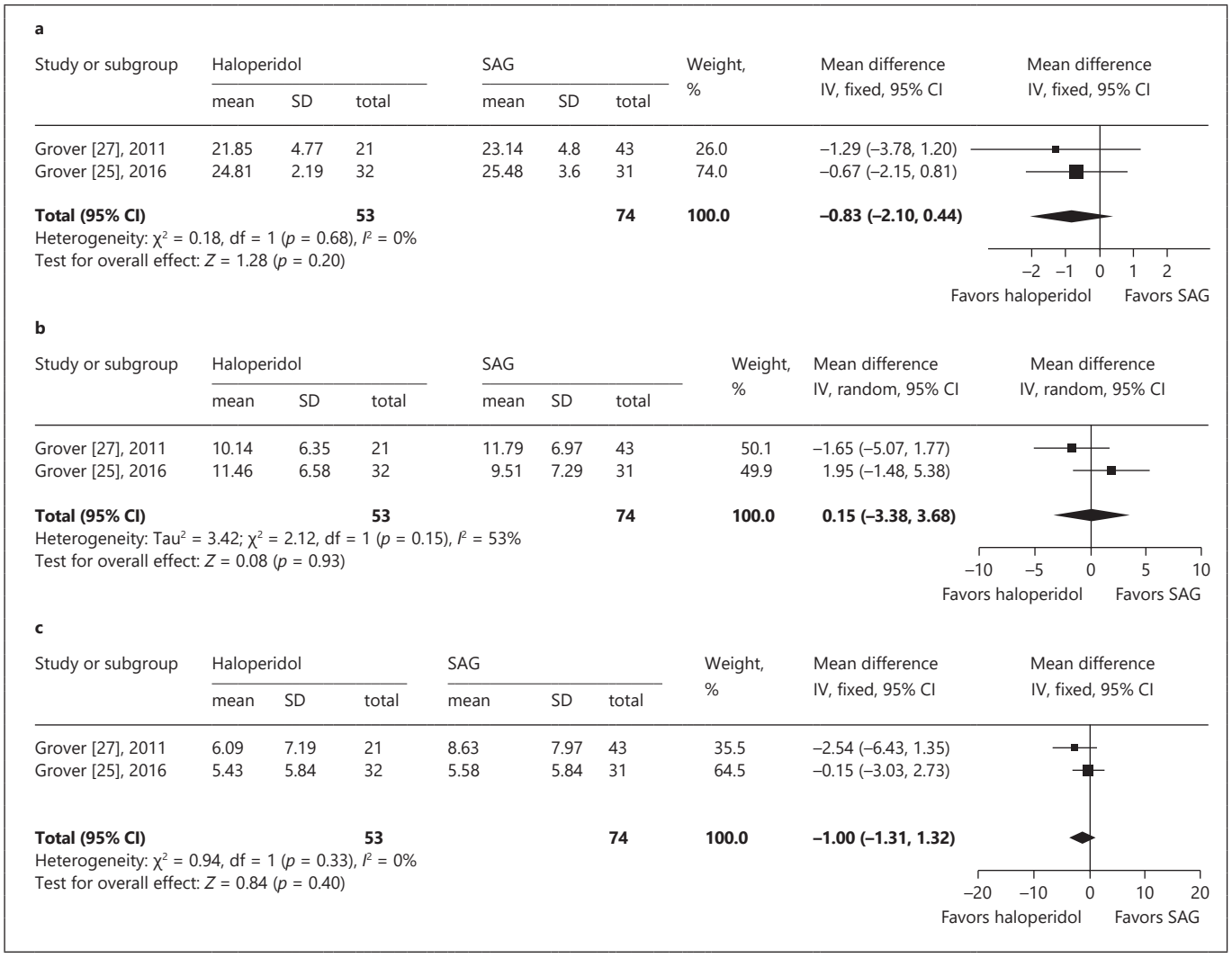

Fig. 5. Meta-analysis of haloperidol versus SGA for DRS-R98 scores at 0 (**a**), 3 (**b**), and 6 (**c**) days. SGA, second-generation antipsychotics.

but the therapy for delirium still needs be tailored to the characteristics of each individual [33–35].

The limitations of this study include the fact that a small number of studies met the inclusion criteria, hence the sample size was relatively small. Further limitations were the heterogeneity of the included studies, the fact that other medications such as dexmedetomidine were reported to have aided in the reduction of postoperative delirium, and the lack of a placebo group for the comparison of haloperidol with second-generation antipsychotics for delirium treatment.

Conclusion

In this systematic review and meta-analysis, haloperidol prophylaxis with a dose of ≥5 mg/day might help reduce the incidence of delirium in surgical patients. For the treatment of delirium, haloperidol exhibited similar effects as the second-generation antipsychotics. However, more studies are required to investigate the optimal regimen for the prophylaxis and treatment of delirium in high-risk patients.

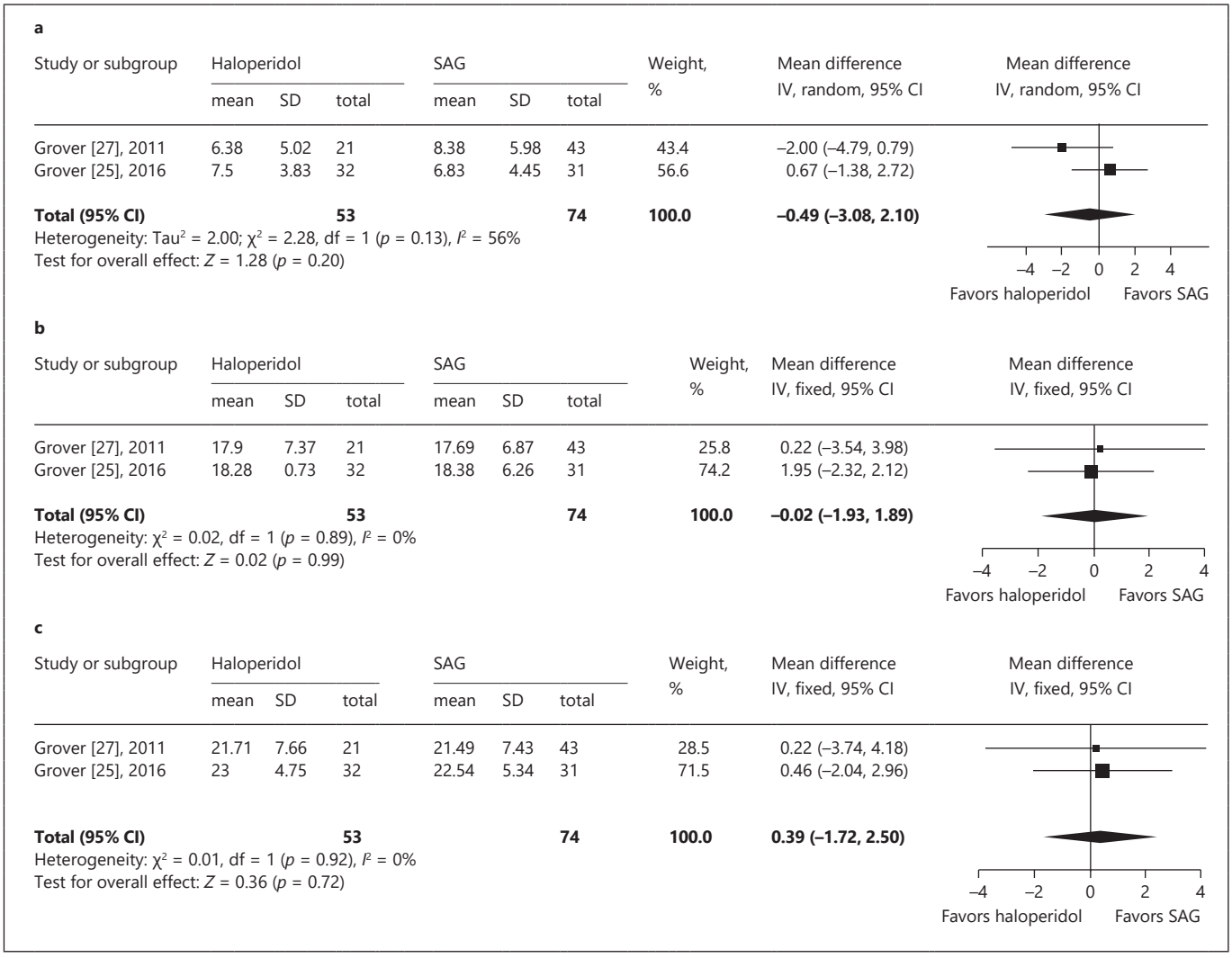

Fig. 6. Meta-analysis of haloperidol versus SGA for MMSE scores at 0 (**a**), 3 (**b**), and 6 (**c**) days. SGA, second-generation antipsychotics.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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