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

Ying-zi Shen Ke Peng Juan Zhang Xiao-wen Meng Fu-hai Ji

Department of Anesthesiology, First Affiliated Hospital of Soochow University, Suzhou, China

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 (\geq 5 mg/day) may help reduce the incidence of delirium in surgical patients (risk ratio 0.50, 95% Cl 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 \geq 5 mg/day might help reduce delirium in adult surgical patients. Further outcome studies with larger sample sizes are required to confirm these findings.

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

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Fu-hai Ji, MD Department of Anesthesiology, First Affiliated Hospital of Soochow University 188 Shizi Street Suzhou, Jiangsu 215006 (China) E-Mail jifuhaisuda@163.com

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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 metaanalysis [22, 23]. Hence, a systematic review and metaanalysis 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 $\leq 50\%$, the fixed-effect model was selected to

Table 1. Characteristics of the included studies

Study	Design	Inclusion criteria (setting)	Exclusion criteria	Interventions (patients, <i>n</i>)	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 (<i>n</i> = 101): 5 mg daily for 5 days after surgery Placebo (<i>n</i> = 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 (<i>n</i> = 32): 0.25-1.25 mg/day Quetiapine (<i>n</i> = 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 Fukata [17], 2014 Fukata [14], 2017 Grover [27], 2011 Grover [25], 2016 Kalisvaart [12], 2005 Kaneko [13], 1999 Page [19], 2013 Schrøder Pedersen [18], 2013 Wang [15], 2012	Low risk Low risk Low risk Low risk Low risk Low risk Low risk High risk Low risk	Low risk Unclear risk Low risk Low risk Low risk Low risk Low risk High risk Low risk	low risk High risk High risk High risk Low risk Unclear risk Low risk High risk Low risk	Low risk Low risk Low risk Low risk Low risk Unclear risk Low risk Unclear risk Low risk Low risk	Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk	Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk	Low risk Low risk 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) sub-group 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

Study or subgroup	Haloper	ridol	Placebo		Weight,	RR	RR		
	events	total	events	total	%	M-H, random, 95% Cl	M-H, random, 95% Cl		
1.1.1 Surgical patients									
Fukata [17], 2014	25	59	20	60	16.7	1.27 (0.80, 2.02)			
Fukata [14], 2017	18	101	32	100	15.5	0.56 (0.34, 0.92)			
Kalisvaart [12], 2005	32	212	36	218	17.5	0.91 (0.59, 1.42)			
(aneko [13], 1999	4	38	13	40	6.6	0.32 (0.12, 0.91)	←─────		
Schrøder Pedersen [18], 2013	22	123	21	117	14.6	1.00 (0.58, 1.71)			
Wang [15], 2012	35	229	53	228	19.0	0.66 (0.45, 0.97)			
Subtotal (95% CI)		762		763	89.9	0.78 (0.58, 1.07)			
Total events	136		175						
Heterogeneity: Tau ² = 0.08; χ^2 Test for overall effect: $Z = 1.09$	= 10.79, 5 (p = 0.1	df = 5 (p 2)	= 0.06), <i>I</i> ² =	54%					
1.1.2 ICU patients	10	24	0	24	10.1	1 50 (0 70 2 20)			
	12	34	ŏ	34	10.1	1.50 (0.70, 3.20)			
Subtotal (95% CI)	10	54	0	54	10.1	1.50 (0.70, 3.20)			
Heterogeneity: Not applicable Lest for overall effect: $7 = 1.0^{\circ}$	$\frac{12}{5(n=0)^2}$	9)	ŏ						
Total (95% CI)	νφ = 0.2	796		797	100.0	0.84 (0.62, 1.13)			
Total events	148		183	- 1		,			
Heterogeneity: $Tau^2 = 0.09$; y^2	= 1327	u = v u	- 11141 1 -	1 1 //1					
Heterogeneity: Tau² = 0.09; χ² Fest for overall effect: Ζ = 1.15 Fest for subgroup differences:	= 13.27, 7 (p = 0.2 2 $\chi^2 = 2.4,$	df = 6 (p 24) 2, df = 1 (j	p = 0.12), I ²	= 58.6%			6.5 0.7 1 1.5 2 Favors haloperidol Favors placebo		
Heterogeneity: Tau ² = 0.09; x ² Fest for overall effect: <i>Z</i> = 1.17 Fest for subgroup differences:	= 13.27, 7 (p = 0.2 : $\chi^2 = 2.4,$	di = 6 (p 24) 2, df = 1 (j	p = 0.12), l ²	= 58.6%			G.S. 0.7 T T.S. 2 Favors haloperidol Favors placebo		
Heterogeneity: Tau ² = 0.09;	= 13.27, 7 (p = 0.2 $\chi^2 = 2.4,$ Haloper	id = 6 (p 2, df = 1 (j idol	$p = 0.12), l^2$ Placebo	= 58.6%	Weight, %	RR M-H, random, 95% Cl	0.5 0.7 I I.5 2 Favors haloperidol Favors placebo RR M-H, random, 95% Cl		
Heterogeneity: Tau ² = 0.09; χ ² Fest for overall effect: <i>Z</i> = 1.13 Fest for subgroup differences: 5 Study or subgroup	$= 13.27, 7 (p = 0.2) \chi^2 = 2.4, Haloper events$	ridol total	$p = 0.12), l^2$ $\frac{\text{Placebo}}{\text{events}}$	= 58.6% total	Weight, %	RR M-H, random, 95% Cl	0.5 0.7 I I.5 2 Favors haloperidol Favors placebo RR M-H, random, 95% Cl		
Heterogeneity: Tau ² = 0.09; X ² Test for overall effect: <i>Z</i> = 1.1; Test for subgroup differences: Study or subgroup 12.1.1 Low doses	$= 13.27, 7 (p = 0.2) 2 \chi^2 = 2.4, Haloper events$	$\frac{di = 6 \ (p)}{2, \ df = 1 \ (p)}$	$p = 0.12), l^2$ $\frac{\text{Placebo}}{\text{events}}$	= 58.6% total	Weight, %	RR M-H, random, 95% Cl	0.5 0.7 I I.5 2 Favors haloperidol Favors placebo RR M-H, random, 95% Cl		
Heterogeneity: Tau ² = 0.09; X ² Test for overall effect: <i>Z</i> = 1.1; Test for subgroup differences: Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016	$= 13.27, 7 (p = 0.2) 7 \chi^2 = 2.4, Haloper events 12$	$\frac{dI = 6 \ (p)}{2, df = 1 \ (p)}$ $\frac{dI = 6 \ (p)}{2, df = 1 \ (p)}$ $\frac{dI = 6 \ (p)}{2, df = 1 \ (p)}$	$p = 0.12), l^2$ $\frac{\text{Placebo}}{\text{events}}$ 8	= 58.6% total	Weight, % 10.1	RR M-H, random, 95% CI 1.50 (0.70, 3.20)	0.5 0.7 I I.5 2 Favors haloperidol Favors placebo RR M-H, random, 95% CI		
leterogeneity: Tau ² = 0.09; χ ² est for overall effect: <i>Z</i> = 1.1; est for subgroup differences: tudy or subgroup 2.1.1 Low doses N-Qadheeb [16], 2016 ukata [17], 2014	$= 13.27, 7 (p = 0.2) 7 (x^2 = 2.4) Haloper events 12 25$	$\frac{dI = 6 \ (p)}{24}$ 2, df = 1 (p) $\frac{idol}{total}$ $\frac{34}{59}$	$p = 0.12), l^2$ $\frac{\text{Placebo}}{\text{events}}$ $\frac{8}{20}$	= 58.6% total 34 60	Weight, % 10.1 16.7	RR M-H, random, 95% CI 1.50 (0.70, 3.20) 1.27 (0.80, 2.02)	G.S. U.7 I I.S. Z Favors haloperidol Favors placebo RR M-H, random, 95% CI		
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Heterogeneity: Tau ² = 0.09; χ^2 Test for overall effect: $Z = 1.1$; Test for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Kalisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04; χ^2 Test for overall effect: $Z = 0.26$	$\begin{array}{r} = 13.27, \\ 7 \ (p = 0.2; \\ \chi^2 = 2.4; \\ \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ \text{id} \\ 2, \ \text{df} = 1 \ (p) \\ \hline \text{total} \\ \hline \\ \hline \\ 123 \\ 229 \\ \textbf{657} \\ \text{df} = 4 \ (p = 30) \\ \hline \end{array}$	$p = 0.12), l^{2}$ $\frac{Placebo}{events}$ 8 20 36 21 53 138 $: 0.17), l^{2} = 3$	total 34 60 218 117 228 657 38%	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9	RR M-H, random, 95% Cl 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28)	RR M-H, random, 95% CI		
Heterogeneity: Tau ² = 0.09; x ² Test for overall effect: <i>Z</i> = 1.1; Test for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Kalisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04; x ² Test for overall effect: <i>Z</i> = 0.26 12.1.2 High doses	= 13.27, 7 (p = 0.2) 7 (p =	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ \text{id} \\ 2, \ \text{df} = 1 \ (p) \\ \hline \text{total} \\ \hline \\ \hline \\ 123 \\ 229 \\ \textbf{657} \\ \text{df} = 4 \ (p = 30) \\ \text{id} \\ \text{id}$	$p = 0.12), l^2$ $\frac{\text{Placebo}}{\text{events}}$ 8 20 36 21 53 138 $: 0.17), l^2 = 3$	total 34 60 218 117 228 657 38%	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9	RR M-H, random, 95% CI 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28)	RR M-H, random, 95% CI		
leterogeneity: Tau ² = 0.09; χ^2 Test for overall effect: $Z = 1.1$; Test for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Kalisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04; χ^2 Test for overall effect: $Z = 0.26$ 12.1.2 High doses Fukata [14], 2017	$= 13.27, 7 (p = 0.2) 7 (p = 0.2) 7 (p = 0.2) 7 (x^2 = 2.4) 7 (p = 0.2) 7 (x^2 = 2.4) 7 (x^2 = 2.4)$	$\frac{\text{ridol}}{\text{total}}$ $\frac{\text{ridol}}{\text{total}}$ $\frac{34}{59}$ 212 123 229 657 df = 4 (p = 30) 101	$p = 0.12), l^{2}$ $\frac{Placebo}{events}$ 8 20 36 21 53 138 : 0.17), l^{2} = 3 32	total 34 60 218 117 228 657 38%	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9 15.5	RR M-H, random, 95% CI 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28) 0.56 (0.34, 0.92)	RR M-H, random, 95% CI		
leterogeneity: Tau ² = 0.09; χ^2 Test for overall effect: $Z = 1.1$; Test for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Kalisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04; χ^2 Test for overall effect: $Z = 0.26$ 12.1.2 High doses Fukata [14], 2017 Kaneko [13], 1999	= 13.27, 7 (p = 0.2) 7 (p =	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ \text{id} \\ 2, \ \text{df} = 1 \ (p) \\ \hline \text{total} \\ \hline \\ \hline \\ 123 \\ 229 \\ \textbf{657} \\ \textbf{657} \\ \text{df} = 4 \ (p = 0) \\ 101 \\ 38 \end{array}$	$p = 0.12), l^{2}$ $\frac{Placebo}{events}$ 8 20 36 21 53 138 0.17), l^{2} = 3 32 13	total 34 60 218 117 228 657 38% 100 40	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9 15.5 6.6	RR M-H, random, 95% Cl 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28) 0.56 (0.34, 0.92) 0.32 (0.12, 0.91)	RR M-H, random, 95% CI		
leterogeneity: Tau ² = 0.09; χ^2 iest for overall effect: $Z = 1.1$; iest for subgroup differences: itudy or subgroup 2.1.1 Low doses N-Qadheeb [16], 2016 ukata [17], 2014 (alisvaart [12], 2005 ichrøder Pedersen [18], 2013 Vang [15], 2012 iubtotal (95% CI) iotal events leterogeneity: Tau ² = 0.04; χ^2 iest for overall effect: $Z = 0.26$ 2.1.2 High doses ukata [14], 2017 (aneko [13], 1999 iubtotal (95% CI)	= 13.27, 7 (p = 0.2) 7 (p =	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ 2, \ \text{df} = 1 \ (p) \\ \hline \text{total} \\ \hline \\ \hline \\ 123 \\ 229 \\ \textbf{657} \\ \textbf{657} \\ \text{df} = 4 \ (p = 30) \\ 101 \\ 38 \\ \textbf{139} \end{array}$	$p = 0.12), l^{2}$ $\frac{Placebo}{events}$ 8 20 36 21 53 138 $: 0.17), l^{2} = 3$ 32 13	total total 34 60 218 117 228 657 38% 100 40 140	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9 15.5 6.6 22.1	RR M-H, random, 95% Cl 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28) 0.56 (0.34, 0.92) 0.32 (0.12, 0.91) 0.50 (0.32, 0.79)	RR M-H, random, 95% CI		
Heterogeneity: $Tau^2 = 0.09$; χ^2 Fest for overall effect: $Z = 1.1$; Fest for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Galisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.04; χ^2 Test for overall effect: $Z = 0.26$ 12.1.2 High doses Sukata [14], 2017 Caneko [13], 1999 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; χ^2	= 13.27, 7 (p = 0.2) 7 (p =	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ 2, \ \text{df} = 1 \ (q) \\ \hline \text{total} \\ \hline \\ \hline \\ 123 \\ 229 \\ \textbf{657} \\ \textbf{657} \\ \text{df} = 4 \ (p = 1) \\ 101 \\ 38 \\ \textbf{139} \\ \textbf{df} = 1 \ (p = 1) \\ (p = $	$p = 0.12), l^{2}$ $\frac{Placebo}{events}$ 8 20 36 21 53 138 $: 0.17), l^{2} = 3$ 32 13 45 $: 0.35), l^{2} = (0.12)$	total total 34 60 218 117 228 657 38% 100 40 140 0%	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9 15.5 6.6 22.1	RR M-H, random, 95% Cl 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28) 0.56 (0.34, 0.92) 0.32 (0.12, 0.91) 0.50 (0.32, 0.79)	RR M-H, random, 95% CI		
Heterogeneity: Tau ² = 0.09; χ^2 Test for overall effect: $Z = 1.1$; Test for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Kalisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04; χ^2 Test for overall effect: $Z = 0.26$ 12.1.2 High doses Fukata [14], 2017 Kaneko [13], 1999 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; χ^2 Total (95% CI)	= 13.27, 7 (p = 0.2) 7 (p =	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ 2, \ \text{df} = 1 \ (p) \\ \hline \text{total} \\ \hline \\ \hline \\ 123 \\ 229 \\ 657 \\ 657 \\ \text{df} = 4 \ (p = 1) \\ 101 \\ 38 \\ 139 \\ \text{df} = 1 \ (p = 1) \\ 796 \\ \end{array}$	$p = 0.12), l^{2}$ $\frac{Placebo}{events}$ 8 20 36 21 53 138 $: 0.17), l^{2} = 3$ 32 13 45 $: 0.35), l^{2} = 0$	total total 34 60 218 117 228 657 38% 100 40 140 0% 797	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9 15.5 6.6 22.1 100.0	RR M-H, random, 95% CI 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28) 0.56 (0.34, 0.92) 0.32 (0.12, 0.91) 0.50 (0.32, 0.79)	RR M-H, random, 95% CI		
Heterogeneity: Tau ² = 0.09; χ^2 Test for overall effect: $Z = 1.1$; Test for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Kalisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04; χ^2 Test for overall effect: $Z = 0.26$ 12.1.2 High doses Fukata [14], 2017 Kaneko [13], 1999 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; χ^2 Fotal (95% CI) Fotal events	= 13.27, 7 (p = 0.2) 7 (p =	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ 2, \ \text{df} = 1 \ (p) \\ \hline \text{total} \\ \hline \\ 123 \\ 229 \\ 657 \\ 657 \\ \text{df} = 4 \ (p = 1) \\ 101 \\ 38 \\ 139 \\ \text{df} = 1 \ (p = 1) \\ 796 \\ \end{array}$	p = 0.04), r = 0.04)	total total 34 60 218 117 228 657 38% 100 40 140 0% 797	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9 15.5 6.6 22.1 100.0	RR M-H, random, 95% CI 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28) 0.56 (0.34, 0.92) 0.32 (0.12, 0.91) 0.50 (0.32, 0.79) 0.84 (0.62, 1.13)	RR M-H, random, 95% CI		
Heterogeneity: Tau ² = 0.09; χ^2 Test for overall effect: $Z = 1.1$; Test for subgroup differences: b Study or subgroup 12.1.1 Low doses Al-Qadheeb [16], 2016 Fukata [17], 2014 Kalisvaart [12], 2005 Schrøder Pedersen [18], 2013 Wang [15], 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04; χ^2 Test for overall effect: $Z = 0.26$ 12.1.2 High doses Fukata [14], 2017 Kaneko [13], 1999 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; χ^2 Total events Heterogeneity: Tau ² = 0.00; χ^2	= 13.27, 7 (p = 0.2) 7 (p =	$\begin{array}{c} \text{id} = 6 \ (p) \\ \text{id} \\ 2, \ \text{df} = 1 \ (p) \\ \hline \text{total} \\ \hline \\ \hline \\ 123 \\ 229 \\ \textbf{657} \\ 65$	p = 0.04), r = 0.04)	total total 34 60 218 117 228 657 38% 100 40 140 0% 797 55%	Weight, % 10.1 16.7 17.5 14.6 19.0 77.9 15.5 6.6 22.1 100.0	RR M-H, random, 95% CI 1.50 (0.70, 3.20) 1.27 (0.80, 2.02) 0.91 (0.59, 1.42) 1.00 (0.58, 1.71) 0.66 (0.45, 0.97) 0.96 (0.73, 1.28) 0.56 (0.34, 0.92) 0.32 (0.12, 0.91) 0.50 (0.32, 0.79) 0.84 (0.62, 1.13)	RR M-H, random, 95% Cl		

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

Study of Subgroup	Halonei		Placebo			Weight	Mean differen	nce Mean difference			Ce.		
	mean	SD	total	mean	SD	total	%	IV, random, 9	5% CI	IV, rand	om, 95%	6 CI	
Al-Qadheeb [16], 2016	2	0.741	34	3	1.481	34	25.7	-1.00 (-1.56, -	-0.44)		_		
Fukata [17], 2014	1.38	2.149	59	1.1	2.047	60	24.6	0.28 (-0.47, 1	.03)		_ _		
Kalisvaart [12], 2005	5.4	4.9	32	11.8	7.5	36	10.3	-6.40 (-9.38, -	-3.42) 👞				
Page [19], 2013	5	4.44	71	5	5.185	70	18.5	0.00 (-1.59, 1	.59)		_	_	
Schrøder Pedersen [18], 2013	4.185	4.095	123	3.75	5.674	117	21.0	0.43 (-0.82, 1	.69)	-			
Total (95% CI)			319			317	100.0	-0.75 (-1.97,	0.46)				
Heterogeneity: Tau ² = 1.41; χ^2	² = 24.75	df = 4 (p < 0.0001),	l ² = 84%	6								
Test for overall effect: $Z = 1.2$	2(p = 0.2)	22)							-4	-2	0	2	4
									Favors	haloperido	ol Fav	ors plac	cebo
b													
Study or subgroup	Halope	ridol	Placeb	D		Weight,	RR				RR		
	events	total	events total		%	M-	H, fixed, 95% CI	M-H, fixed, 95% C			5 CI		
Al-Qadheeb [16], 2016	4	34	1	3	34	8.3	4.00) (0.47, 33.97)			-		
Page [19], 2013	7	71	6	7	70	50.1	1.1	5 (0.41, 3.25)		_			
Wang [15], 2012	4	229	5	22	28	41.6	0.8	0 (0.22, 2.93)					
Total (95% CI)		334		33	32	100.0	1 2	4 (0 59 2 59)					
							1.4	+ (0.55, 2 .55)			-		
Total events	15		12				1.2	(0.55, 2.55)			-		
Total events Heterogeneity: χ^2 = 1.62, df =	15 = 2 (p = 0	.45), <i>I</i> ² =	12 0%				1.2	+ (0.00, 2.00)	0.01	0.1	1	10	100
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$	15 = 2 (p = 0 7 (p = 0.5	.45), <i>I</i> ² = 57)	12 0%				1.2		0.01 Favors ha	0.1 iloperidol	1 Favors	10 placeb	100 00
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$	15 = 2 (p = 0 7 (p = 0.5	.45), <i>I</i> ² = 57)	12 0%				1.2	((,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	0.01 Favors ha	0.1 Noperidol	1 Favors	10 placeb	100 00
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup	15 2 (p = 0 7 (p = 0.5 Haloper	.45), I ² = 57) ridol	12 0% Placebo	0		Weight,	RR	. (0.00, 2.00)	0.01 Favors ha	0.1	Favors RR	10 placeb	100
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup	15 $2 (p = 0)$ $7 (p = 0.5)$ $\frac{\text{Haloper}}{\text{events}}$.45), <i>I</i> ² = 57) ridol total	12 0% Placebi events	o to	otal	Weight, %	RR M-I	H, fixed, 95% CI	0.01 Favors ha	0.1 Noperidol M-H, fix	RR ked, 95%	10 placeb	100
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup Al-Qadheeb [16], 2016	15 $2 (p = 0)$ $7 (p = 0.5)$ $\frac{\text{Halopen}}{\text{events}}$ 1	$\frac{(45)}{(7)}, l^2 = \frac{1}{57}$	12 0% Placebr events 0	o to	tal	Weight, % 14.2	RR M-1 3.00	H, fixed, 95% Cl	0.01 Favors ha	0.1 loperidol M-H, fix	Favors RR ked, 95%	n placeb 5 CI	100
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup Al-Qadheeb [16], 2016 Page [19], 2013	15 $= 2 (p = 0)$ $7 (p = 0.5)$ $\frac{\text{Halopere}}{\text{events}}$ 1 2	$(.45), l^2 =, l^2$ ridol total 34 71	12 0% Placebu events 0 3	o to	tal 34 70	Weight, % 14.2 85.8	RR M-1 3.00	H, fixed, 95% Cl (0.13, 71.15) 5 (0.11, 3.81)	0.01 Favors ha	0.1 Noperidol M-H, fix	Favors RR ked, 95%	10 placeb	100 po
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup Al-Qadheeb [16], 2016 Page [19], 2013 Wang [15], 2012	15 $2 (p = 0 7 (p = 0.5)$ $\frac{\text{Haloperend}}{\text{events}}$ 1 2 0	$\frac{(45)}{17}, l^2 = \frac{1}{57}$	12 	0 to 3 7 22	-tal 34 70 28	Weight, % 14.2 85.8	RR M-1 3.00 0.61 No	H, fixed, 95% Cl (0.13, 71.15) 5 (0.11, 3.81) t estimable	0.01 Favors ha	0.1 Iloperidol M-H, fix	RR ked, 95%	n 10 5 placeb 5 Cl	100 po
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup Al-Qadheeb [16], 2016 Page [19], 2013 Wang [15], 2012	$ \begin{array}{r} 15 \\ 2 \ (p = 0 \\ 7 \ (p = 0.5 \\ \end{array} $ $ \begin{array}{r} Haloper events \\ 1 \\ 2 \\ 0 \\ \end{array} $	$\frac{(.45)}{100}, l^2 = \frac{1}{57}$	12 0% Placeby events 0 3 0	0 to 3 7 22	tal 34 70 28	Weight, % 14.2 85.8	RR M-1 3.00 0.66 No ⁻	H, fixed, 95% Cl 0 (0.13, 71.15) 5 (0.11, 3.81) t estimable	0.01 Favors ha	0.1 loperidol M-H, fiz	RR ked, 95%	10 placeb	100 po
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup Al-Qadheeb [16], 2016 Page [19], 2013 Wang [15], 2012 Total (95% CI)	$ \begin{array}{r} 15 \\ 2 \ (p = 0) \\ 7 \ (p = 0.5) \\ \hline \hline 4 \\ \hline events \\ 1 \\ 2 \\ 0 \end{array} $	(45), l ² = 57) ridol total 34 71 229 334	12 0% Placebi events 0 3 0	0 to 3 7 22	otal 34 70 28 32	Weight, % 14.2 85.8 100.0	RR M-1 3.00 0.60 No	H, fixed, 95% Cl 0 (0.13, 71.15) 5 (0.11, 3.81) t estimable 9 (0.23, 4.25)	0.01 Favors ha	0.1 N-H, fix	RR ked, 95%	10 placeb	100 po
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup Al-Qadheeb [16], 2016 Page [19], 2013 Wang [15], 2012 Total (95% CI) Total events	$ \begin{array}{r} 15 \\ 2 \ (p = 0) \\ 7 \ (p = 0.5) \\ \hline $	(45), l ² = (7) ridol total 34 71 229 334	12 0% Placebi events 0 3 0 3	0 to 3 7 22 33	otal 34 70 28 32	Weight, % 14.2 85.8 100.0	RR M-1 3.00 0.60 No	H, fixed, 95% Cl 0 (0.13, 71.15) 5 (0.11, 3.81) t estimable 9 (0.23, 4.25)	0.01 Favors ha	0.1 N-H, fix	RR ked, 95%	10 placeb	100 po
Total events Heterogeneity: $\chi^2 = 1.62$, df = Test for overall effect: $Z = 0.5$ c Study or subgroup Al-Qadheeb [16], 2016 Page [19], 2013 Wang [15], 2012 Total (95% CI) Total events Heterogeneity: $\chi^2 = 0.68$, df =	$ \begin{array}{r} 15 \\ 2 \ (p = 0) \\ 7 \ (p = 0.5) \\ \hline $	$\frac{(45)}{(77)}, l^{2} = \frac{1}{(77)}$	12 0% Placebi events 0 3 0 3 0%	0 to 3 7 22 33	atal 34 70 28 32	Weight, % 14.2 85.8 100.0	RR M-1 3.00 0.60 No	H, fixed, 95% Cl 0 (0.13, 71.15) 5 (0.11, 3.81) t estimable 9 (0.23, 4.25)	0.01 Favors ha	0.1 N-H, fix	RR ked, 95%	10 placeb 5 Cl	100 po

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 ($\geq 5 \text{ mg/day}$) 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

а										
Study or subgroup	Halope	eridol		Placebo			Weight,	Mean difference	Mean difference	
	mean	SD	total	mean	SD	total	%	IV, fixed, 95% Cl	IV, fixed, 95% Cl	
Al-Qadheeb [16], 2016	6.5	2.963	34	7	3.704	34	24.1	-0.50 (-2.09, 1.09)		
Page [19], 2013	5	4.44	71	5	5.185	70	24.1	0.00 (-1.59, 1.59)		
Wang [15], 2012	2.003	7.64	229	2.025	3.488	228	51.8	-0.02 (-1.11, 1.07)		
Total (95% CI) Heterogeneity: $\chi^2 = 0.27$, df =	2(p = 0.3)	87), <i>I</i> ² = 0	334 %			332	100.0	-0.13 (-1.91, 0.65)	•	
Test for overall effect: $Z = 0.33$	s(p = 0.7)	4)						-4	-2 0 2 4	
								Favors h	aloperidol Favors placebo	
b										
Study or subgroup	Haloper	idol		Placebo			Weight,	RR	RR	
	mean	SD	total	mean	SD	total	%	M-H, random, 95% Cl	M-H, random, 95% Cl	
Kalisvaart [12], 2005	17.1	11.1	32	22.6	16.7	36	28.2	-5.50 (-12.17, 1.17)		
Page [19], 2013	18.5	14.074	71	26	18.519	70	33.4	-7.50 (-12.93, -2.07)	_ e	
Wang [15], 2012	24.5	20.632	229	24.09	26.561	228	38.4	0.41 (-3.95, 4.77)		
Total (95% CI) Heterogeneity: $Tau^2 = 13.30$: x	² = 5.49.	df = 2 (n	332 = 0.06), <i>[</i> *	= 64%		334	100.0	-3.90 (-9.09, 1.29)	-	
Test for overall effect: $Z = 1.47$	7 (p = 0.1)	4)						-20	-10 0 10 20	
								Favors h	aloperidol Favors placebo	
c										
Study or subgroup	Haloperidol			Placebo		Weight,		RR	RR	
	events	total	e	vents	total	%		M-H, fixed, 95% Cl	M-H, fixed, 95% Cl	
Al-Qadheeb [16], 2016	9	34		7	34	20.7	,	1.29 (0.54, 3.06)		
Page [19], 2013	20	71	1	9	70	56.6	5	1.04 (0.61, 1.77)	_ # _	
Schrøder Pedersen [18], 2013	5	123		4	117	12.1		1.19 (0.33, 4.32)		
Wang [15], (2012)	0	35		4	53	10.6	5	0.17 (0.01, 3.00) <		
Total (95% CI)		263			274	100.0)	1.01 (0.67, 1.55)		
Total events	34		3	4						
Heterogeneity: $\chi^2 = 1.85$, df =	3(p = 0.6)	60), $I^2 = 0$	1%					0.05		
Test for overall effect: $Z = 0.07$	7 (p = 0.9	5)						Favors h	aloperidol Favors placebo	
									•	

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,

	Haloper	ridol		SAG			Weight,	Mean difference	Mean difference	
	mean	SD	total	mean	SD	total	%	IV, fixed, 95% CI	IV, fixed, 95% CI	
Grover [27], 2011 Grover [25], 2016	21.85 24.81	4.77 2.19	21 32	23.14 25.48	4.8 3.6	43 31	26.0 74.0	-1.29 (-3.78, 1.20)		
Total (95% CI) Heterogeneity: $\chi^2 = 0$ Test for overall effec	0.18, df = ´ t: <i>Z</i> = 1.28	1 (p = 0.6 (p = 0.20	53 8), <i>I</i> ² = 0%			74	100.0	-0.83 (-2.10, 0.44) Favor	-2 -1 0 1 2 shaloperidol Favors S	
b										
Study or subgroup	Haloper	ridol		SAG			— Weight, — %	Mean difference	Mean difference	
	mean	SD	total	mean	SD	total		IV, random, 95% Cl	IV, random, 95% Cl	
Grover [27], 2011 Grover [25], 2016	10.14 11.46	6.35 6.58	21 32	11.79 9.51	6.97 7.29	43 31	50.1 49.9	-1.65 (-5.07, 1.77) 1.95 (-1.48, 5.38)		
Total (95% Cl) Heterogeneity: Tau ²	= 3.42; χ ² :	= 2.12, df	53 = 1 (p = 0.	15), <i>l</i> ² = 53%		74	100.0	0.15 (-3.38, 3.68)		
Test for overall effec	t: Z = 0.08	φ = 0.95						–10 Favors	–5 0 5 haloperidol Favors SA	
Test for overall effec c Study or subgroup	t: Z = 0.08 Haloper	φ = 0.93		SAG			Weight,	10 Favors Mean difference	–5 0 5 haloperidol Favors SA Mean difference	
Test for overall effec c Study or subgroup	t: Z = 0.08 Haloper mean	ridol	total	SAG mean	SD	total	Weight, %	ר–ית Favors Mean difference IV, fixed, 95% Cl	–5 0 5 haloperidol Favors SA Mean difference IV, fixed, 95% Cl	
c Study or subgroup Grover [27], 2011 Grover [25], 2016	Haloper mean 6.09 5.43	ridol SD 7.19 5.84	total 21 32	SAG mean 8.63 5.58	SD 7.97 5.84	total 43 31	Weight, % 35.5 64.5	10 Favors Nean difference IV, fixed, 95% CI -2.54 (-6.43, 1.35) -0.15 (-3.03, 2.73)	n −5 0 5 haloperidol Favors S/ Mean difference IV, fixed, 95% CI	

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.

а											
Study or subgroup	Halope	eridol		SAG			Weight, %	Mean difference IV, random, 95% Cl	Mean difference		
	mean	SD	total	mean	SD	total			IV, random, 95% Cl		
Grover [27], 2011 Grover [25], 2016	6.38 7.5	5.02 3.83	21 32	8.38 6.83	5.98 4.45	43 31	43.4 56.6	-2.00 (-4.79, 0.79) 0.67 (-1.38, 2.72)			
Total (95% CI) Heterogeneity: Tau ² Test for overall effec	= 2.00; χ² t: <i>Z</i> = 1.28	= 2.28, 3 (p = 0.	53 df = 1 (p = 20)	0.13), <i>I</i> ² =	56%	74	100.0	-0.49 (-3.08, 2.10)	-4 -2 0 2 4 Favors haloperidol Favors SAC		
b											
Study or subgroup	Halope	eridol		SAG			– Weight,	Mean difference	Mean difference		
	mean	SD	total	mean	SD	total	70	TV, fixed, 95% Cl	IV, IIXeu, 95% CI		
Grover [27], 2011 Grover [25], 2016	17.9 18.28	7.37 0.73	21 32	17.69 18.38	6.87 6.26	43 31	25.8 74.2	0.22 (–3.54, 3.98) 1.95 (–2.32, 2.12)			
Total (95% CI) Heterogeneity: $\chi^2 = 0$ Test for overall effect	0.02, df = t: <i>Z</i> = 0.02	1 (p = 0 2 (p = 0.	53 0.89), <i>I</i> ² = 0 ⁴ 99)	%		74	100.0	-0.02 (-1.93, 1.89)	-4 -2 0 2 Favors haloperidol Favors SAG		
Study or subgroup	Halope	eridol		SAG			Weight,	Mean difference	Mean difference IV, fixed, 95% Cl		
	mean	SD	total	mean	SD	total	- %	IV, fixed, 95% CI			
Grover [27], 2011 Grover [25], 2016	21.71 23	7.66 4.75	21 32	21.49 22.54	7.43 5.34	43 31	28.5 71.5	0.22 (-3.74, 4.18) 0.46 (-2.04, 2.96)			
Total (95% CI) Heterogeneity: $\chi^2 = 0$ Test for overall effect	0.01, df = t: <i>Z</i> = 0.36	1 (p = 0 5 (p = 0.	53).92), <i>I</i> ² = 0 ⁴ 72)	%		74	100.0	0.39 (–1.72, 2.50)	-4 -2 0 2 4 Favors haloperidol Favors SAG		

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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