ORIGINAL ARTICLE

Penhyclidine Hydrochloride Premedication Is Not Associated with Increased Incidence of Post-Operative Cognitive Dysfunction or Delirium: A Systemic Review and Meta-Analysis

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Key words: penhyclidine hydrochloride; post-operative cognitive dysfunction; post-operative delirium; meta-analysis

Objective Post-operative cognitive dysfunction (POCD) and post-operative delirium (POD) are two common post-operative cerebral complications. The current meta-analysis was to systematically review the effects of penhyclidine hydrochloride (PHC) on POCD and POD in surgical patients.

Methods Electronic databases were searched to identify all randomized controlled trials comparing PHC with atropine/scopolamine/placebo on POCD and POD in surgical patients. Primary outcomes of interest included the incidences of POCD and POD; the secondary outcomes of interest included peri-operative mini-mental state examination (MMSE) scores. Two authors independently extracted peri-operative data, including patients' baseline characteristics, surgical variables, and outcome data. For dichotomous data (POCD and POD occurrence), treatment effects were calculated as odds ratio (OR) and 95% confidential interval (CI). Each outcome was tested for heterogeneity, and randomized-effects or fixed-effects model was used in the presence or absence of significant heterogeneity. For continuous variables (MMSE scores), treatment effects were calculated as weighted mean difference (WMD) and 95% CI. Statistical significance was defined as $P < 0.05$.

Results Our search yielded 33 studies including 4 017 patients. Meta-analysis showed that, the incidence

of POCD in PHC group was comparable to that in saline group ($OR=0.97$; 95% CI : 0.58-1.64; $P=0.92$), scopolamine group ($OR=0.78$; 95% CI : 0.48-1.27; $P=0.32$) and atropine group ($OR=1.20$; 95% CI : 0.86-1.67; $P=0.29$). The incidence of POD in PHC group was comparable to that in saline group ($OR=1.53$; 95% CI : 0.81-2.90; $P=0.19$) and scopolamine group ($OR=0.53$; 95% CI : 0.06-4.56; $P=0.56$), but higher than that in atropine group ($OR=4.49$; 95% CI : 1.34-15.01; $P=0.01$).

Conclusions PHC premedication was not associated with increased incidences of POCD or POD as compared to either scopolamine or placebo.

POST-OPERATIVE cognitive dysfunction (POCD) and post-operative delirium (POD) are two common post-operative cerebral complications, with the incidence ranging from 8.9% to 46.1% for POCD and 13.2% to 41.7% for POD, respectively.^[1-6] Post-operative cognitive deficits could cause severe problems and increase morbidity and mortality.^[1-6] The exact pathogenesis of POCD and POD remains to be determined, but could be multifactorial.^[1-6] Acetylcholine (ACh) is a neurotransmitter associated with awareness and cognitive function, and anti-cholinergic medications may increase the risk of cognitive impairment.^[7] Anticholinergic drugs have been used as premedication before surgery for their antisialogogue, vagolytic, antiemetic, sedative and amnesic effects for quite a long time. Scopolamine premedication also has sedative effect and could produce a central anti-cholinergic syndrome (e.g., confusion, agitation, delirium, drowsiness, and coma).^[8,9] Atropine can cause similar but less potent central effects.^[9]

Penahyclidine hydrochloride (PHC), a new anti-cholinergic drug developed by the Institute of Pharmacology and Toxicology affiliated to the Chinese Academy of Military Medical Sciences, has potent central and peripheral anti-cholinergic effects.^[10,11] Different from scopolamine and atropine, PHC selectively blocks M1, M3 and N receptors, and has few M2 receptor-associated cardiovascular side effects.^[10,11] Preliminary evidence suggested that PHC could also provide pulmonary and gastrointestinal protection in surgical patients.^[12-15] Currently, PHC is used widely in China as a premedication prior to anesthesia and surgery. However, it remains unknown whether PHC premedication increase the incidence of POCD and POD. Therefore, we performed the present meta-analysis, aiming to establish the relationship between PHC premedication and the occurrence of POD and POCD.

MATERIALS AND METHODS

Search strategy

We conducted a systemic review according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) Guidelines.^[16] The protocol of current meta-analysis was published in PROSPERO with the registration number of CRD42019125183. Relevant trials were identified by computerized searches of MEDLINE, Cochrane Library and EMBASE till December 26th 2018 (see online *Appendix*). No language restriction was used. We also searched Chinese BioMedical Literature & Retrieval System (CBM), China National Knowledge Infrastructure (CNKI), VIP and Wangfang Data (from inception to December 26th 2018). Additionally, we used the bibliography of retrieved articles to further identify relevant studies.

Study inclusion criteria

We included all randomized controlled trials (RCT) comparing PHC with controls (atropine/scopolamine/placebo), as well as those comparing different doses of PHC, with respect to the incidences of POCD and POD in surgical patients. Data of all groups were abstracted from all finally included studies. Primary outcomes of interest included the incidences of POCD and POD. Secondary outcomes of interest included peri-operative mini-mental state examination (MMSE) scores. Exclusion criteria included: 1) studies published as review, case report or abstract; 2) animal studies; 3) duplicate publications; 4) studies lacking information about outcomes of interest. Two authors (YH and FNX) independently reviewed the titles and abstracts of all identified studies for eligibility, and excluded obviously ineligible ones. The eligibility of the remaining studies for final inclusion was further determined by reading the full text.

Study quality assessment

The *Jadad* score was used independently by two au-

thors (YH and FNX) to evaluate the methodological quality of each included trial. The *Jadad* scoring system (ranging from 0 to 5) includes: 1) randomization process; 2) blindedness assessment; and 3) reporting of withdrawals/dropouts. Higher scores indicate excellent methodologic qualities, and lower scores suggest poor qualities.^[17]

Data abstraction

The following data were abstracted from the included studies to a data collection form by two authors (YH and FNX) independently: 1) first author, year of publication and the journal; 2) total number of patients, number of patients in PHC group and control groups respectively; 3) surgical procedure; 4) data regarding outcomes of interest. Disagreements were resolved by discussion among all authors during the process of data abstraction. The authors of the included studies were contacted if necessary.

Statistical analysis

All data were analyzed by utilizing RevMan (version 5.3, Cochrane). Pooled odds ratio (*OR*) and 95% confidence interval (*CI*) were estimated for dichotomous data, and weighted mean difference (*WMD*) and 95% *CI* for continuous data, respectively. Each outcome was tested for heterogeneity, and randomized-effects or fixed-effects model was used in the presence or absence of significant heterogeneity (*Q*-statistical test, $P < 0.05$). Sensitivity analyses were done by examining the influence of statistical model on estimated treatment effects, and analyses which adopted the fixed-effects model were repeated again by using randomized-effects model and *vice versa*. In addition, sensitivity analysis was performed to evaluate the influence of individual study on the overall effects. Publication bias was explored through visual inspection of funnel plots of the outcomes. All *P* values were two-sided and statistical significance was defined as $P < 0.05$.

RESULTS

Search results

As depicted in the flow chart (**Figure 1**), database search identified 50 articles for complete evaluation. Finally, 33 eligible trials^[18-50], all written in Chinese, were included in the meta-analysis. Patients' characteristics, surgery information and quality assessment results were presented in **Table 1**. There

was a wide spectrum of surgical procedures in the included trials, ranging from non-cardiac to cardiac surgeries, from extremity procedure to thoracic operation. Some trials involved patients with multiple surgical procedures.

Characteristics of included studies

As shown in **Table 2**, the 33 eligible trials involved 4 017 patients in total, and 2 497 patients were allocated into PHC group, 792 into atropine group, 260 into scopolamine group and 468 into placebo (saline) group. PHC administration protocols (dosage, timing and route) varied among included trials. PHC dosages ranged from 0.002 mg/kg to 0.020 mg/kg, or 0.25 mg to 1.00 mg. PHC were administered 5 - 40 min before anesthesia intravenously, intramuscularly, or intranasally. Of the 33 trials, 22 reported the occurrence of POCD, all based upon Mini Mental State Examination (MMSE) scores. Among the 12 trials reporting POD, POD was diagnosed by Confusion Assessment Method (CAM) in 6 studied, by psychiatrist in 1 study,^[34] and no diagnosis criteria in five studies. Among the 33 eligible trials, 27 compared the occurrence of POCD or POD between PHC and other comparators (Atropine, Scopolamine, Placebo). Fifteen trials compared the occurrence of POCD or POD among different doses of PHC, 6 out of which only compared among different doses of PHC.

Quality of included studies

As shown in **Table 1**, 8 trials^[31,33,35-37,45,48,49] had *Jadad* score of 3 and were considered as high-quality RCTs, and the other 25 trials^[18-30,32,34,38-44,46,47,50] were scored at 2. Five^[36,37,45,48,49] out of the 33 trials described their

Figure 1. Flow chart of literature selection.

Table 1. Patients and surgery data of the included studies ($n = 33$)

Study	Surgery	Patient characteristics			Comparator drug(s)	Jadad assessment		
		Age (years)	Education	ASA		Random-ization	Blind-ness	With-drawals
Bi <i>et al.</i> , 2012 ^[34]	Ortho, Uro	75-89	>High school	II - III	Scopolamine	1	0	1
Chen <i>et al.</i> , 2011 ^[19]	Ex, Ab	>65	6-9 years	I - III	Saline	1	0	1
Guo <i>et al.</i> , 2010 ^[20]	Ex, Ab	20-59	6-9 years	I - II	Atropine	1	0	1
Guo <i>et al.</i> , 2014 ^[50]	Ab	61-73	NR	NR	Penethyclidine	1	0	1
Hu <i>et al.</i> , 2015 ^[48]	Thorax	61-80	NR	II - III	Penethyclidine	2	0	1
Kong <i>et al.</i> , 2010 ^[39]	Ab	≥60	>9 years	I - II	Atropine/Scopolamine/Saline	1	0	1
Li <i>et al.</i> , 2008 ^[24]	NCS	>60	NR	I - II	Atropine	1	0	1
Li <i>et al.</i> , 2009 ^[31]	LC	65-75	Illiteracy	I - III	Saline	1	1	1
Li <i>et al.</i> , 2010 ^[22]	NCS	>60	NR	I - IV	Atropine	1	0	1
Li <i>et al.</i> , 2012 ^[21]	LC	60-80	NR	I - III	Penethyclidine	1	0	1
Liao <i>et al.</i> , 2017 ^[44]	Ortho	≥60	NR	I - II	Atropine/Saline	1	0	1
Liu <i>et al.</i> , 2009 ^[29]	NCS	>65	NR	I - II	Atropine	1	0	1
Liu <i>et al.</i> , 2013 ^[26]	NCS	60-85	NR	I - III	Atropine	1	0	1
Liu <i>et al.</i> , 2014 ^[46]	NR	52-79	NR	NR	Penethyclidine	1	0	1
Liu <i>et al.</i> , 2015 ^[25]	Thyroid	18-85	NR	I - II	Atropine/Saline	1	0	1
Liu <i>et al.</i> , 2016 ^[49]	NCS	34-67	NR	II - III	Penethyclidine	2	0	1
Lv <i>et al.</i> , 2009 ^[35]	Maxillo-facial	61-79	Mixed	I - III	Atropine	1	1	1
Shu <i>et al.</i> , 2009 ^[27]	NCS	65-78	NR	II - III	Atropine/Scopolamine	1	0	1
Shu <i>et al.</i> , 2013 ^[47]	NCS	65-78	NR	II - III	Penethyclidine	1	0	1
Tang <i>et al.</i> , 2010 ^[38]	CS	15-55	NR	II - III	Saline	1	0	1
Wang <i>et al.</i> , 2013 ^[33]	Mixed	35-60	NR	II - III	Scopolamine	1	1	1
Wang <i>et al.</i> , 2017 ^[32]	Thorax	43-65	NR	I - II	Saline/Ulinastatin	1	0	1
Wu <i>et al.</i> , 2010 ^[18]	Ab	65-75	>9 years	II - III	Saline	1	0	1
Wu <i>et al.</i> , 2014 ^[40]	Ab	60-83	NR	I - III	Scopolamine	1	0	1
Xia <i>et al.</i> , 2017 ^[36]	NCS	60-78	NR	I - III	Atropine	2	0	1
Xiang <i>et al.</i> , 2011 ^[42]	Thorax, Ab	60-80	NR	NR	Atropine	1	0	1
Xu <i>et al.</i> , 2008 ^[28]	Ab	>65	>9 years	I - III	Saline	1	0	1
Yang <i>et al.</i> , 2011 ^[43]	LC	64-70	NR	NR	Atropine	1	0	1
Ye <i>et al.</i> , 2011 ^[41]	Ex	65-90	NR	I - III	Atropine/Saline	1	0	1
Ye <i>et al.</i> , 2015 ^[45]	LC	65-80	>5 years	I - II	Saline	2	0	1
Yu <i>et al.</i> , 2011 ^[23]	Vocal cord	31-70	NR	I - II	Atropine/Scopolamine	1	0	1
Zhang <i>et al.</i> , 2012 ^[30]	NCS	>65	>9 years	I - III	Saline	1	0	1
Zou <i>et al.</i> , 2017 ^[37]	NCS	65-76	NR	I - III	Atropine	2	0	1

Ortho, orthopedic; Uro, urologic; Ab, abdominal; LC, laproscopic cholecystectomy; NCS, non-cardiac surgery; ENT, ear-nose-throat; Ex, extremity; ASA, American Society of Anesthesiologists; NR, not reported. Trials were arranged in alphabetic order of the first authors' name and the publication year.

randomization method and 3 trials^[31,33,35] reported blindness method.

Incidences of POCD and POD

Eight trials (724 patients)^[18,19,28, 30,38,39,41,44], 4 trials (450 patients)^[27,34,39,40] and 8 trials (781 patients)^[26,27,29,35,36,39,41,44] compared the effect of PHC

versus saline, scopolamine and atropine with respect to the incidence of POCD, respectively. As in **Figure 2** and **Table 3**, meta-analysis showed that the incidence of POCD in PHC group was comparable to that in saline group [23.4% (90/385) *vs.* 24.2% (82/339), *OR* = 0.97; 95% *CI*: 0.58-1.64; *P* = 0.92], Scopolamine group [16.7% (45/270) *vs.* 22.2% (40/180),

Table 2. PHC administration scheme and reported outcomes of the included trials ($n=33$)

Studies	Sample size	Groups (n)	PHC group				Control group			Outcomes reported		
			n	Dose	Route	Timing	n	Comparator	Dose	POCD	POD	MMSE
Bi <i>et al.</i> , 2012 ^[34]	90	3	30	0.002 mg/kg	iv	After iv access	30	Scopolamine	0.002 mg/kg	√	-	√
Chen <i>et al.</i> , 2011 ^[19]	124	3	42	0.5 mg	iv	10' BA	42	Saline	Same volume	√	-	√
			40	1.0 mg	iv							
Guo <i>et al.</i> , 2010 ^[20]	300	6	50	0.008 mg/kg	im	10' BA	50	Atropine	0.08 mg/kg	√	-	√
			50	0.01 mg/kg								
			50	0.012 mg/kg								
			50	0.014 mg/kg								
			50	0.016 mg/kg								
Kong <i>et al.</i> , 2010 ^[39]	320	4	78	1.0 mg	im	30' BA	80	Saline	Same volume	√	-	√
							80	Scopolamine	0.3 mg			
							82	Atropine	0.5 mg			
Li <i>et al.</i> , 2008 ^[24]	80	2	40	0.01 mg/kg	iv	30' BA	40	Atropine	0.01 mg/kg	-	√	-
Li <i>et al.</i> , 2009 ^[31]	120	3	40	0.5 mg	iv	10' BA	40	Saline	Same volume	-	√	√
			40	1.0 mg								
Li <i>et al.</i> , 2010 ^[22]	289	3	98	0.01 mg/kg	im	30' pre-op	96	Atropine	0.01 mg/kg	-	√	-
			95	0.02 mg/kg								
Liao <i>et al.</i> , 2017 ^[44]	144	3	48	1.0 mg	im	30' pre-op	48	Blank	-	√	√	-
							48	Atropine	0.5 mg			
Liu <i>et al.</i> , 2009 ^[29]	60	2	30	0.5 mg	im	30' pre-op	30	Atropine	0.5 mg	√	-	√
Liu <i>et al.</i> , 2013 ^[26]	60	2	30	0.5 mg	iv	10' BA	30	Atropine	0.5 mg	√	-	√
Liu <i>et al.</i> , 2015 ^[25]	116	4	29	0.01 mg/kg	iv	30' BA	29	Saline	Same volume	-	-	√
			29	0.02 mg/kg			29	Atropine	0.06 mg/kg			
Lv <i>et al.</i> , 2009 ^[35]	120	2	60	0.01 mg/kg	iv	30' pre-op	60	Atropine	0.01 mg/kg	√	-	√
Shu <i>et al.</i> , 2009 ^[27]	120	3	40	0.5 mg	im	30' BA	40	Scopolamine	0.3 mg	√	-	√
							40	Atropine	0.5 mg			
Tang <i>et al.</i> , 2010 ^[38]	40	2	20	0.015 mg/kg	im	30' BA	20	Saline	Same volume	√	-	√
Wang <i>et al.</i> , 2013 ^[33]	60	2	30	1.0 mg	im	Pre-op	30	Scopolamine	0.3 mg	-	√	-
Wang <i>et al.</i> , 2017 ^[32]	60	2	30	0.02 mg/kg	iv	15' BA	30	Saline	Same volume	-	-	√
Wu <i>et al.</i> , 2010 ^[18]	71	2	40	0.5 mg	iv	10' BA	31	Saline	Same volume	√	√	√
Wu <i>et al.</i> , 2014 ^[40]	120	4	30	0.005 mg/kg	im	40' BA	30	Scopolamine	0.006 mg/kg	√	√	-
			30	0.01 mg/kg								
			30	0.02 mg/kg								

Continued Table 2. PHC administration scheme and reported outcomes of the included trials ($n=33$)

Studies	Sample size	Groups (n)	PHC group				Control group			Outcomes reported		
			n	Dose	Route	Timing	n	Comparator	Dose	POCD	POD	MMSE
Xia <i>et al.</i> , 2017 ^[36]	90	2	45	0.5 mg	iv	10' BA	45	Atropine	0.5 mg	√	-	√
Xiang <i>et al.</i> , 2011 ^[42]	80	2	40	1.0 mg	im	30' pre-op	40	Atropine	0.5 mg	-	-	√
Xu <i>et al.</i> , 2008 ^[28]	80	2	42	0.5 mg	iv	10' BA	38	Saline	Same volume	√	√	√
Yang <i>et al.</i> , 2011 ^[43]	64	2	32	0.01-0.02 mg/kg	im	40' BA	32	Atropine	0.008-0.01 mg/kg	-	-	√
Ye <i>et al.</i> , 2011 ^[41]	180	3	60	1.0 mg	im	30' BA	60	Saline	Same volume	√	-	√
							60	Atropine	0.5 mg			
Ye <i>et al.</i> , 2015 ^[45]	60	3	20	0.01 mg/kg	iv	30' BA	20	Saline	Same volume	√	-	√
			20	0.02 mg/kg								
Ye <i>et al.</i> , 2015 ^[45]	241	4	80	0.5 mg	iv	40' BA	50	Scopolamine	0.3 mg	-	√	-
			61	1.0 mg			50	Atropine	0.5 mg			
Zhang <i>et al.</i> , 2012 ^[30]	60	2	30	0.02 mg/kg	iv	10' BA	30	Saline	Same volume	√	√	-
Zou <i>et al.</i> , 2017 ^[37]	120	2	60	0.5 mg	iv	10' BA	60	Atropine	0.5 mg	-	-	√
Guo <i>et al.</i> , 2014 ^[50]	60	3	20	0.004 mg/kg	im	30' BA		-		√	-	√
			20	0.008 mg/kg								
			20	0.012 mg/kg								
Hu <i>et al.</i> , 2015 ^[48]	146	2	73	0.005 mg/kg	iv	30' BA		-		√	-	√
			73	0.015 mg/kg								
Li <i>et al.</i> , 2012 ^[21]	120	4	30	0.25 mg	iv	5' BA		-		√	√	√
			30	0.50 mg								
			30	0.75 mg								
			30	1.00 mg								
Liu <i>et al.</i> , 2014 ^[46]	200	5	40	0.008 mg/kg	iv	30' BA		-		√	√	-
			40	0.011 mg/kg								
			40	0.014 mg/kg								
			40	0.017 mg/kg								
			40	0.020 mg/kg								
Liu <i>et al.</i> , 2016 ^[49]	102	3	34	0.50 mg	in	20' BA		-		-	-	√
			34	1.00 mg								
			34	1.50 mg								
Shu <i>et al.</i> , 2013 ^[47]	120	3	40	0.005 mg/kg	iv	30' BA		-		√	-	√
			40	0.010 mg/kg								
			40	0.015 mg/kg								

Pre-op, pre-operatively; BA, before anesthesia; POCD, post-operative cognitive dysfunction; POD, post-operative delirium; MMSE, mini-mental state examination; PHC, penehyclidine hydrochloride; iv, intravenously; im, intramuscularly; in, intranasally.

Figure 2. Forest plot of meta-analyses comparing premedication effects of penethyclidine with saline, scopolamine and atropine on POCD incidence.

Table 3. Comparison of incidences of POCD and POD between groups of penethyclidine and controls

Incidence of the outcomes (%)	Trials (<i>n</i>)	Group PHC (<i>n</i>)	Group Control (<i>n</i>)	Heterogeneity		Analysis model	<i>OR</i>	95% <i>CI</i>	Overall effect <i>P</i>
				<i>I</i> ² (%)	<i>P</i>				
POCD									
Penethyclidine vs. Saline	8	385	339	50	0.05	M-H, random	0.97	0.58,1.64	0.92
Penethyclidine vs. Scopolamine	4	270	180	22	0.28	M-H, fixed	0.78	0.48,1.27	0.32
Penethyclidine vs. Atropine	8	389	392	48	0.06	M-H, fixed	1.20	0.86,1.67	0.29
POD									
Penethyclidine vs. Saline	3	162	109	0	0.62	M-H, fixed	1.53	0.81,2.90	0.19
Penethyclidine vs. Scopolamine	2	171	80	82	0.02	M-H, random	0.53	0.06,4.56	0.56
Penethyclidine vs. Atropine	3	374	186	0	0.90	M-H, fixed	4.49	1.34,15.01	0.01

M-H, Mantel-Haenszel; OR, odds ratio, CI, confidence interval.

$OR=0.78$; 95% CI : 0.48-1.27; $P=0.32$] and Atropine group [24.9% (97/389) vs. 21.7%(85/392), $OR=1.20$; 95% CI : 0.86 - 1.67 ; $P=0.29$].

Three trials(271 patients),^[18,28,31] 2 trials(251 patients)^[23,33] and 3 trials(560 patients)^[22-24] compared the effect of PHC *versus* saline, scopolamine and atropine with respect to the incidence of POD, respectively. As in **Figure 3** and **Table 3**, meta-analysis showed that the incidence of POD in PHC group was comparable to that in Placebo group [23.5% (38/162) vs.16.5%(18/109), $OR=1.53$; 95% CI : 0.81 - 2.90; $P=0.19$] and Scopolamine group [9.9% (17/171) vs. 21.3%(17/80), $OR=0.53$; 95% CI : 0.06 - 4.56; $P=0.56$], but higher than that in Atropine group [7.8% (29/374) vs. 1.6% (3/186), $OR=4.49$; 95% CI : 1.34 - 15.01; $P=0.01$].

MMSE scores

Nine trials (883 patients),^[18,19,25,30-32,39,41,44] 5 trials (411 patients),^[20,25,32,39,44] 4 trials (338 patients)^[19,32,34,39], 5 trials (317 patients)^[30-32,44,50], 1 trial(120 patients)^[45] and 2 trials(229 patients)^[18,39] compared MMSE scores

of PHC *versus* Placebo group before operation (base-line), on post-operative day(POD)-1, POD-2, POD-3, POD-5, and POD-7, respectively. As shown in **Table 4**, no significant intergroup difference in MMSE scores was found in each comparisons.

Three trials (356 patients),^[27,39,40] 5 trials (356 patients),^[19,27,34,39,40] 5 trials (356 patients),^[19,27,34,39,40] 4 trials (200 patients)^[19,27,34,40] and 1 trial (156 patients)^[39] compared MMSE scores of PHC *versus* scopolamine group before operation, on POD-1, POD-2, POD-3, POD-7, respectively. As shown in **Table 4**, no significant intergroup difference in MMSE scores was found in each comparisons.

Twelve trials (1317 patients),^[20,25-27,31,36,37,39,41-44] 8 trials (773 patients),^[25-27,36,37,39,42,44] 3 trials (360 patients),^[27,37,39] 4 trials (386 patients),^[27,36,37,44] 2 trials (420 patients)^[20,41] and 5 trials (424 patients)^[26,31,39,42,43] compared MMSE scores of PHC *versus* atropine group before operation, on POD-1, POD-2, POD-3, POD-5, POD-7, respectively. As shown in **Table 4**, no significant intergroup difference in MMSE scores was found in each comparisons.

Figure 3. Forest plot of meta-analyses comparing premedication effects of penethyclidine with saline, scopolamine and atropine on POD incidences.

Table 4. Comparison of MMSE scores of POD between the PHC group and the control groups

Outcomes	Trials (<i>n</i>)	Group PHC (<i>n</i>)	Group Control (<i>n</i>)	Heterogeneity		Analysis model	WMD	95% <i>CI</i>	Overall effect <i>P</i>
				<i>I</i> ² (%)	<i>P</i>				
Penehyclidine vs. Saline									
Pre-op	9	493	390	0	0.97	IV, fixed	0.10	-0.11,0.31	0.34
POD1	5	214	197	95	<0.00001	IV, random	-0.22	-1.82,1.38	0.79
POD2	4	187	151	95	<0.00001	IV, random	0.14	-1.62,1.90	0.88
POD3	5	178	139	89	<0.00001	IV, random	-0.68	-1.87,0.51	0.26
POD5	1	60	60	NA	NA	IV, random	-2.30	-2.87,-1.73	<0.00001
POD7	2	118	111	0	0.55	IV, fixed	0.07	-0.37,0.52	0.75
Penehyclidine vs. Scopolamine									
Pre-op	3	208	148	57	0.05	IV, random	0.11	-0.17,0.39	0.44
POD1	3	208	148	97	<0.00001	IV, random	0.88	-0.36,2.13	0.17
POD2	3	208	148	95	<0.00001	IV, random	0.87	-0.04,1.78	0.06
POD3	2	130	70	71	0.02	IV, random	-0.12	-0.51,0.27	0.54
POD5	0	NA	NA	NA	NA	NA	NA	NA	NA
POD7	1	78	78	NA	NA	IV, random	0.20	-0.30,0.70	0.44
Penehyclidine vs. Atropine									
Pre-op	12	771	546	40	0.04	IV, fixed	-0.02	-0.18,0.13	0.78
POD1	8	399	374	81	<0.00001	IV, random	-0.38	-1.09,0.32	0.29
POD2	3	178	182	4	0.35	IV, fixed	-0.16	-0.55,0.22	0.41
POD3	4	193	193	81	0.001	IV, random	-0.23	-1.20,0.74	0.64
POD5	2	310	110	79	0.0002	IV, random	0.95	-1.09,3.00	0.36
POD7	5	210	214	96	<0.00001	IV, Random	-0.74	-2.57,1.08	0.42

POD1, POD2, POD3, POD5, and POD7 means post-operative day 1, day 2, day 3, day 5 and day 7, respectively. IV, inverse variance; WMD, weighted mean difference; NA, not available.

Dose-effects of PHC on POCD and POD

As shown in **Table 5**, meta-analysis demonstrated that PHC premedication, when given at 1.0 mg, significantly increased the incidence of POD [21.4% (28/131) vs. 10.0% (15/150), *OR*=2.36; 95% *CI*: 1.19-4.69; *P*=0.01] and the incidence of POD concurrent with POCD [25.0% (50/200) vs. 9.5% (21/220), *OR*=3.05; 95% *CI*: 1.75-5.29; *P*<0.0001] as compared to 0.5 mg, but did not increase the incidence of POCD alone [31.9%(22/69) vs. 8.6%(6/70), *OR*=6.00; 95% *CI*: 0.67-53.51; *P*=0.11].

PHC premedication when given at 0.02mg/kg, as compared to 0.01 mg/kg, significantly increased the incidences of POD [15.6%(21/135) vs. 3.6%(5/138), *OR*=0.20; 95% *CI*: 0.07-0.56; *P*=0.002], POCD [32.2% (29/90) vs. 10.0%(9/90), *OR*=0.23; 95% *CI*: 0.10-0.53; *P*=0.0005], and the concurrence [22.2% (50/225) vs. 6.1%(14/228), *OR*=0.22; 95% *CI*: 0.12-

0.41; *P*<0.00001].

No significant difference was observed with respect to PHC premedication at the dosage of 0.01 mg/kg as compared to 0.015 mg/kg in the incidences of POD, POCD, and the concurrence; comparing between the dosage of 0.01 mg/kg and 0.008 mg/kg, no significant difference was observed in the incidence of either POD or POCD, with a slightly significant difference observed in the incidence of the concurrence [12.0% (12/100) vs. 4.0% (4/100), *OR*=3.39; 95% *CI*:1.05-10.98; *P*=0.04]; comparing between the dosage of 0.01 mg/kg and 0.005mg/kg, no significant difference was observed in the incidence of either POCD or the concurrence of POD and POCD.

Sensitivity analysis and publication bias

Sensitivity analysis showed that treatment effects on all the outcomes were not affected by statistical model

Table 5. Incidences of POCD, POD, and POCD+POD compared between different PHC dosages

Outcomes	Trials (<i>n</i>)	Dosage 1 Events/Patients	Dosage 2 Events/Patients	Heterogeneity		Analysis model	OR	95% CI	Overall effect <i>P</i>
				<i>I</i> ² (%)	<i>P</i>				
		1.0 mg	0.5 mg						
POCD	2	22/69	6/70	56	0.13	M-H, random	6.00	0.67,53.51	0.11
POD	3	28/131	15/150	0	0.78	M-H, fixed	2.36	1.19,4.69	0.01
POCD+POD	4	50/200	21/220	0	0.52	M-H, fixed	3.05	1.75,5.29	<0.0001
		0.01 mg/kg	0.02 mg/kg						
POCD	3	9/90	29/90	0	0.82	M-H, fixed	0.23	0.10,0.53	0.0005
POD	2	5/138	21/135	0	0.96	M-H, fixed	0.20	0.07,0.56	0.002
POCD+POD	4	14/228	50/225	0	0.98	M-H, fixed	0.22	0.12,0.41	<0.00001
		0.01 mg/kg	0.015 mg/kg						
POCD	2	13/80	18/80	0	0.56	M-H, fixed	0.66	0.29,1.48	0.31
POD	1	2/40	2/40	NA	NA	NA	1.00	0.13,7.47	1.00
POCD+PD	2	15/120	20/120	0	0.79	M-H, fixed	0.70	0.33,1.47	0.34
		0.01 mg/kg	0.008 mg/kg						
POCD	2	10/60	4/60	0	0.98	M-H, fixed	3.09	0.86,11.08	0.08
POD	1	2/40	2/40	NA	NA	NA	5.26	0.24,113.11	0.29
POCD+POD	2	4/100	12/100	0	0.95	M-H, fixed	3.39	1.05,10.98	0.04
		0.01 mg/kg	0.005 mg/kg						
POCD	3	22/90	13/90	31	0.23	M-H, fixed	1.95	0.90,4.22	0.09
POD	0	0	0	NA	NA	NA	NA	NA	NA
POCD+POD	3	22/90	13/90	31	0.23	M-H, fixed	1.95	0.90,4.22	0.09

(Table 6). To analyze the influence of the overall treatment effect on high heterogeneity outcomes, we also performed sensitivity tests with exclusion of some studies, and no contradictory results were found. There was no significant publication bias detected by funnels plot examination for the incidence of either POCD or POD (Figure 4).

DISCUSSION

Evidence suggested that exposure to anticholinergic agents may increase the risk of cognitive impairment and all-cause mortality in the elderly.^[7] Currently, routine use of anticholinergic premedication has greatly decreased worldwide. In some countries, the anticholinergic prophylaxis is directed to eye-nose-throat (ENT) and eye surgeries, endoscopic proce-

dures and to children younger than 1 year old.^[51]

PHC, a new generation of anticholinergic drug with less unwanted cardiovascular effects, is widely used as premedication in China. With its ether-based structure containing a non-quaternary ammonium cation, PHC could easily pass the blood-brain barrier^[10, 11] to have cerebral effects, such as sedation, amnesia. Liang and colleagues^[52] reported that PHC premedication administered at a dose of 0.012mg/kg could reduce propofol dosage for anesthesia induction without effect on Bispectral index (BIS) values. The recent trial by Wang *et al.*^[53] demonstrated that preoperative intravenous administration of PHC at 0.01 mg/kg reduced the incidence of intra-operative awareness in patients undergoing breast cancer surgery during general anesthesia. Premedication with either scopolamine or atropine could result in POCD and POD. While

Table 6. Influence of statistical model on estimated treatment effects of primary outcomes

Statistical model	OR (95% CI) of POCD			OR (95% CI) of POD		
	PHC vs. SAL	PHC vs. SCO	PHC vs. ATR	PHC vs. SAL	PHC vs. SCO	PHC vs. ATR
Fixed effects	0.98 (0.69,1.38)	0.78 (0.48,1.27)	1.20 (0.86,1.67)	1.56 (0.83,2.93)	0.53 (0.24,1.16)	4.51 (1.35,15.08)
Random effects	0.97 (0.58,1.64)	0.73(0.40,1.32)	1.13 (0.70,1.83)	1.53 (0.81,2.90)	0.53 (0.06,4.56)	4.49 (1.34,15.01)

SAL, saline; SCO, scopolamine; ATR, atropine.

Figure 4. Funnel plots assess for publication bias in the incidences of POCD and POD.

the effect of PHC premedication on POCD and POD still remains unknown. In the cohort study by Mu *et al.*,^[54] multivariate logistic regression analysis suggested PHC premedication to be an independent predictor of early POCD after coronary artery bypass graft (CABG) surgery. In contrast, the present meta-analysis demonstrated that PHC premedication might not be associated with increased risks of either POCD or POD when compared to saline or scopolamine.

POD and POCD are separate entities but often intricate, being a phenomenon logically supported by a common pathologic cause (*i.e.*, post-operative neuroinflammation).^[1-6,55] Unlike the late onset of POCD (weeks or sometimes months), POD usually occurs during the initial post-operative period, after a free interval of only a few hours or days from the operation.^[1,55] The duration of delirium is generally short (1-3 days) whereas POCD can last for several months, sometimes even longer.^[2,6,55] POCD and POD also share some common risk factors, such as aging (*e.g.*, >65 yrs), pre-existing cognitive impairment, specific types of surgery.^[1-6] There are a number of diagnostic tools designed to aid in the diagnosis of delirium. The Confusion Assessment Method (CAM) has been found to have very high sensitivity, specificity and inter-rater reliability.^[2,3,6] The incidence and duration of POD may be easy to determine with the CAM — which was used by trials in the current meta-analysis. The diagnosis of POCD is much more complex than that of POD.^[1,6] Unlike the diagnosis of POD with CAM, a POCD diagnosis can only be achieved by the comparison between pre- and post-operative testings.^[5,6] Till now, no consensus has been made on which test be applied in the diagnosis of POCD. The International Study of Postoperative Cognitive Dys-

function (ISPOCD) group recommended a battery of neuropsychological tests to diagnose POCD.^[56] MMSE is a useful tool for cognitive evaluation and can be administered in less than 10 minutes.^[57] Actually, MMSE was designed to screen severe global cognitive deficits present in dementia, not well suitable for the selective and slight deficits of POCD.^[3,5,6,57] However, many studies including those trials in the current meta-analysis used MMSE to diagnose POCD.

Our meta-analysis also demonstrated that PHC premedication when given at dose of 1.0 mg could significantly increase the incidence of POD and PD compared to the dose of 0.5 mg, and that PHC premedication when given at 0.02 mg/kg, could significantly increase the incidence of POD and PD compared to the dose of 0.01 mg/kg, suggesting that the cognitive effect of PHC could be dose-dependent. The Phase II clinical trial observing the tolerability and safety of PHC in healthy subjects recommend that the maximal tolerant dosage of PHC tablet is 0.8 mg daily and the dose regimen of 0.6 mg daily for multiple doses.^[58] Recently, the dose range from 0.005 mg/kg to 0.01 mg/kg has been recommended as expert opinion for PHC premedication to be effective without increasing the risk of POD.^[59] Whether there is an optimal dose of PHC which could minimize detrimental cognitive influence without decreasing its premedication effectiveness remains to be determined. This study has the weakness inherent in meta-analysis. Meta-analysis can increase the power of analysis by pooling many small studies, but variances (patient characteristics, surgery type, diagnosis criteria of cognitive impairment, *etc.*) and varied quality of included studies may limit the certainty of the findings of meta-analysis. To clarify the

influence of PHC on the occurrence of POCD and POD in surgical patients, prospective randomized, placebo-controlled, triple-blinded trials are warranted.

To conclude, this meta-analysis suggested that, PHC premedication was not associated with increased incidence of POCD or POD as compared to scopolamine or placebo.

Conflict of interest

None.

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