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Meta-Analysis

The advantages of penehyclidine hydrochloride over atropine in acute organophosphorus pesticide poisoning: A meta-analysis

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ABSTRACT

Background: Penehyclidine hydrochloride (PHC) has been used for many years as an anticholinergic drug for the treatment of acute organophosphorus pesticide poisoning (AOPP). The purpose of this meta-analysis was to explore whether PHC has advantages over atropine in the use of anticholinergic drugs in AOPP.

Methods: We searched Scopus, Embase, Cochrane, PubMed, ProQuest, Ovid, Web of Science, China Science and Technology Journal Database (VIP), Duxiu, Chinese Biomedical literature (CBM), WanFang, and Chinese National Knowledge Infrastructure (CNKI), from inception to March 2022. After all qualified randomized controlled trials (RCTs) were included, we conducted quality evaluation, data extraction, and statistical analysis. Statistics using risk ratios (RR), weighted mean difference (WMD), and standard mean difference (SMD).

Results: Our meta-analysis included 20,797 subjects from 240 studies across 242 different hospitals in China. Compared with the atropine group, the PHC group showed decreased mortality rate (RR=0.20, 95% confidence intervals [CI]: 0.16–0.25, P <0.001), hospitalization time (WMD=−3.89, 95% CI: −4.37 to −3.41, P <0.001), overall incidence rate of complications (RR=0.35, 95% CI: 0.28–0.43, P <0.001), overall incidence of adverse reactions (RR=0.19, 95% CI: 0.17–0.22, P <0.001), total symptom disappearance time (SMD=−2.13, 95% CI: −2.35 to −1.90, P <0.001), time for cholinesterase activity to return to normal value 50–60% (SMD=−1.87, 95% CI: −2.03 to −1.70, P <0.001), coma time (WMD=−5.57, 95% CI: −7.20 to −3.95, P <0.001), and mechanical ventilation time (WMD=−2.16, 95% CI: −2.79 to −1.53, P <0.001).

Conclusion: PHC has several advantages over atropine as an anticholinergic drug in AOPP.

Introduction

Organophosphorus pesticides (OP) have been used as pesticides for nearly two centuries.[1] The World Health Organization estimates that OP causes poisoning in 3 million people worldwide every year, of which about 300,000 die.[2] The majority of people poisoned by OP live in developing countries, especially the rural areas. Suicide deaths from consuming pesticides account for one-third of global suicides every year, which results in great pressure on world public health.[3]

An important pathophysiological mechanism of acute organophosphorus pesticide poisoning (AOPP) is the inhibition of acetylcholinesterase by poisons, which results in the accumulation of endogenous acetylcholine, causing the continuous impulse of cholinergic nerves. The clinical manifestations of this phenomenon are muscarinic symptoms (massive sweating, tears, salivation, bradycardia, bronchospasm, pulmonary edema); nicotine symptoms (muscle fiber fibrillation, tonic spasm); and central nervous system symptoms (dizziness, headache, irritability, delirium, and coma).[4] Patients may die suddenly because of obstruction of the airway by a large volume of respiratory secretions, bronchospasm, and pulmonary edema. Up to now, the detoxification treatment of AOPP is still cholinesterase reactivators based on oximes to restore

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the cholinesterase activity and anticholinergic drugs based on atropine to block excessive acetylcholine at the neuromuscular junctions in the human body.[3] Atropine, a traditional anticholinergic drug that antagonizes cholinergic receptors, has been used as an anticholinergic drug for AOPP since the 1950s. A common cause of death in AOPP patients is central nervous system toxicity.[5] However, atropine does not antagonize the central nervous system cholinergic receptors and systemic nicotine receptors.[6] In addition, the sensitivity of patients to atropine varies greatly across the population. Although the use of optimal doses of atropine in AOPP can reduce mortality, it is clinically challenging to determine the correct dose.[7] This often results in atropine poisoning or insufficient treatment dose.[8] Moreover, in patients with underlying diseases and elderly patients, an important cause of death in AOPP patients is the adverse reaction of atropine [5,9].

At the end of the 20th century, China developed penehyclidine hydrochloride (PHC), a new long-acting anticholinergic drug that can antagonize both muscarinic as well as nicotinic receptors. At the same time, it can cross the blood–brain barrier and play a key role in antagonizing central cholinergic receptors; hence, PHC is considered to have unique pharmacological characteristics that atropine lacks.[5] Since the introduction of PHC, hundreds of hospitals in China have used it to treat AOPP and achieved good therapeutic results. Since 2000, a large number of academic conferences on emergency or poisoning held in China have repeatedly proposed the benefits of PHC in the treatment of AOPP [10–28]. Several randomized controlled trials (RCTs) have shown that in the anticholinergic treatment of AOPP, atropine is expected to be replaced by PHC [29–38]. Thus far, there are only three relevant Chinese meta-analyses published during 2010–2012 that have shown that PHC has advantages over atropine in the treatment of AOPP. However, they included fewer studies, the quality of included studies was low, and the meta-analyses had inherent biases [39–41]. Only one meta-analysis published in English showed that PHC combined with atropine could reduce mortality in AOPP.[8] Due to insufficient evidence-based clinical findings, the latest expert consensus did not propose PHC as the first choice of anticholinergic drug in the treatment of AOPP.[42] The purpose of this meta-analysis is to summarize all published RCTs and explore whether PHC has advantages over atropine as an anticholinergic drug in AOPP. We believe the summary of this analysis may provide useful clinical evidence for the next version of expert consensus.

Methods

We registered this meta-analysis on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) in March 2022 with a digital object identifier (DOI) of 10.37766/inplasy2022.3.0133 (registration number: 202230133). This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Database and search strategies

According to the retrieval methods of different databases, our team formulated detailed advanced retrieval strategies. We retrieved five Chinese databases, namely China Science and Technology Journal Database (VIP), Duxiu, Chinese Biomedical literature (CBM), WanFang, and Chinese National Knowledge Infrastructure (CNKI), and seven English databases, namely Scopus, Embase, Cochrane, PubMed, ProQuest, Ovid, and Web of Science. We also searched whether there are corresponding clinical trials in clinical trial centers in China and the United States. The search date range of articles in the above databases was from the establishment of the database to March 17, 2022. In the Chinese search term, we used four different variants for "acute organophosphorus pesticide poisoning." For "penehyclidine," three variants were used – penehyclidine hydrochloride, penehyclidine, and its trade name Changtuoning. For the type of experiment, our key words included random control, random distribution, random, RCT, lottery, random number table, and computer random. For the retrieval of English database, we used subject words and free words to retrieve the corresponding articles within the scope of RCTs, in which medical subject headings (MeSH) terms included organophosphate poisoning and penehyclidine. The literature search and screening were performed by two different reviewers each. If there were differences, other reviewers in the team participated in the discussion and finally reached an agreement. Search strategies are listed in Supplementary Appendix 1.

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) The subjects were AOPP patients, who were poisoned in various forms. (2) In the study, the experimental group used PHC, and the control group used atropine. General treatments such as gastric lavage, emesis induction, catharsis, adsorption of toxins, and application of oximes were the same in the experimental group and the control group in each study. (3) Articles reported one or more of the following: mortality rate, hospitalization time, the overall incidence rate of complications, incidence of delayed polyneuropathy, intermediate syndrome, rebound, and respiratory failure; the overall incidence of adverse reactions, incidence of blurred vision, thirst, urinary retention, tachycardia, fever, restlessness, and disturbance of consciousness; the total symptom disappearance time, disappearance time of muscarinic symptoms, nicotinic symptoms, and central nervous system symptoms; time for cholinesterase activity to return to normal value of 50–60%, coma time, and mechanical ventilation time. (4) Articles were searched from inception to March 2022. (5) Articles published in Chinese or English. (6) All articles were tested on adults.

The exclusion criteria are as follows: (1) non-RCT design. (2) The articles were reviews or meta-analyses. (3) Nursing articles. (4) Articles were not available. (5) The articles were not rigorous. (6) The patient suffers from some other condition or disease such as severe trauma or infectious diseases.

Data extraction

Because this study involves a large number of articles, four reviewers extracted the data and another four checked them to prevent data errors. We designed a table to extract the following information from each included article: first author, publication year, journal name, database, sample size, gender composition, average age or age windows, time from onset to visit or the time

windows, degree of poisoning, intervention and control methods, and outcomes.

Quality assessment

According to the indicators of the Cochrane Collaboration tool, three reviewers evaluated all included articles one by one. If they were unable to reach an agreement, the first author rejoined the discussion until a consensus was reached.

Statistical analysis

The flow chart of literature screening and quality evaluation were completed by Review Manager 5.3. With regard to statistical analysis, because of the large number of documents included, Stata (version 16) was used to make forest plots. For continuous variables, weighted mean difference (WMD), standard mean difference (SMD), and 95% confidence intervals (CI) were reported, and for dichotomous variables, risk ratios (RR) were reported. The I^2 test was used for the degree of heterogeneity; if I^2 <50%, the heterogeneity was considered small and a fixed-effects model was used, but if I^2 >50%, the heterogeneity was considered large and a random effects model was used. Some outcome indicators have different units. If there were a large number of studies in different units, we use SMD to pool effect sizes. If the number of studies in different units were small, we directly converted their units into the units of most studies to pool effect size. Egger's test was used to test for publication bias for several major outcome indicators. If there was publication bias, the trim and fill method was used to correct and test whether the results were robust.

Results

Literature screening

At the beginning, we retrieved 2765 articles from 12 databases; no articles were retrieved from the two clinical trial centers. After deleting duplicate articles, 769 articles remained. Among them, the intervention measures or control measures of 319 articles were inconsistent, and 82 articles did not match the outcome indicators. In addition, 16 articles were on animal experiments, 11 articles were reviews or meta-analysis, 19 articles were on nursing, and the subjects of 14 articles were children. After excluding the above articles, 308 remained. Furthermore, the full-text of 2 articles could not be obtained, 5 articles contained duplicate data, 23 articles did not have relevant data, and 18 articles had imprecise data; all these were also excluded. Finally, after excluding 20 more articles that were not RCTs, the remaining 240 articles [29–38,43–272] were included in this meta-analysis.The flow chart of literature screening is presented in Figure 1.

General information of each study

These 240 RCTs, from 2000 to 2021, recruited a total of 20,797 patients from 242 different hospitals in China. Of these, 10,685 subjects were assigned to the PHC group and 10,112 to the atropine group. The two groups' basic treatment measures were the same, including defecation, diuresis, dehydration, use of oximes, and other comprehensive treatments. For patients who needed mechanical ventilation, endotracheal intubation and ventilator were provided to assist with ventilation. The baseline characteristics of the two groups in each study were the same (P >0.05). Supplementary Table 1 shows the clinical and demographic details of each study. The usage of PHC and atropine in the two groups of each study is shown in Supplementary Table 2.

Quality assessment

After evaluation by three reviewers, a consistent conclusion was finally reached. Of all 240 studies, only 36 explicitly used specific randomized methods and only 1 article used the allocation concealment method. All three reviewers agreed that the results of each study were not affected by performance bias. With regard to the detection bias, only 3 studies were clearly double-blind trials, and other studies were determined to be unclear. None of the 240 studies had loss of follow-up and missing data; thus, in attrition bias, they all were judged as low risk. Five studies had selective reports and were judged as high risk. In addition, the reporting bias of seven studies was rated unclear. Due to insufficient information, all 240 studies were rated unclear on other biases. Figure 2 shows the specific quality assessment chart of included studies.

Outcomes

The summary of all outcomes is shown in Table 1.

Mortality rate

Mortality rate refers to the ratio of the number of patients who died during hospitalization to the total number of patients. A total of 76 studies reported mortality rates: I^2=0.0%, which indicated zero heterogeneity; hence, we used the fixed effect model, which showed that the PHC group could significantly reduce the mortality (RR=0.20, 95% CI: 0.16–0.25, and P <0.001, Figure 3). The P-value of Egger's test was <0.05, which showed publication bias. Using the trim and fill method, the final correction result was not very different from the previous results, indicating that the result was robust (RR=0.25, 95% CI: 0.04–0.46, and P <0.001).

Hospitalization time

A total of 145 studies reported hospitalization time. Because only 4 studies were measured in hours, we converted them into days and combined the statistics: I^2=98.1%, which indicated large heterogeneity, and so we used the random effect model, which showed that the PHC group could significantly reduce the hospitalization time (WMD = −3.89, 95% CI: −4.37 to −3.41, and P <0.001, Supplementary Figure 1). The P-value of Egger's test was 0.010 < 0.05, which showed publication bias. The correction result of the trim and fill method was not very different from the previous results, which meant that the impact of publication bias was small and the result was robust (WMD=−4.55, 95% CI: −4.99 to −4.11, P <0.001).

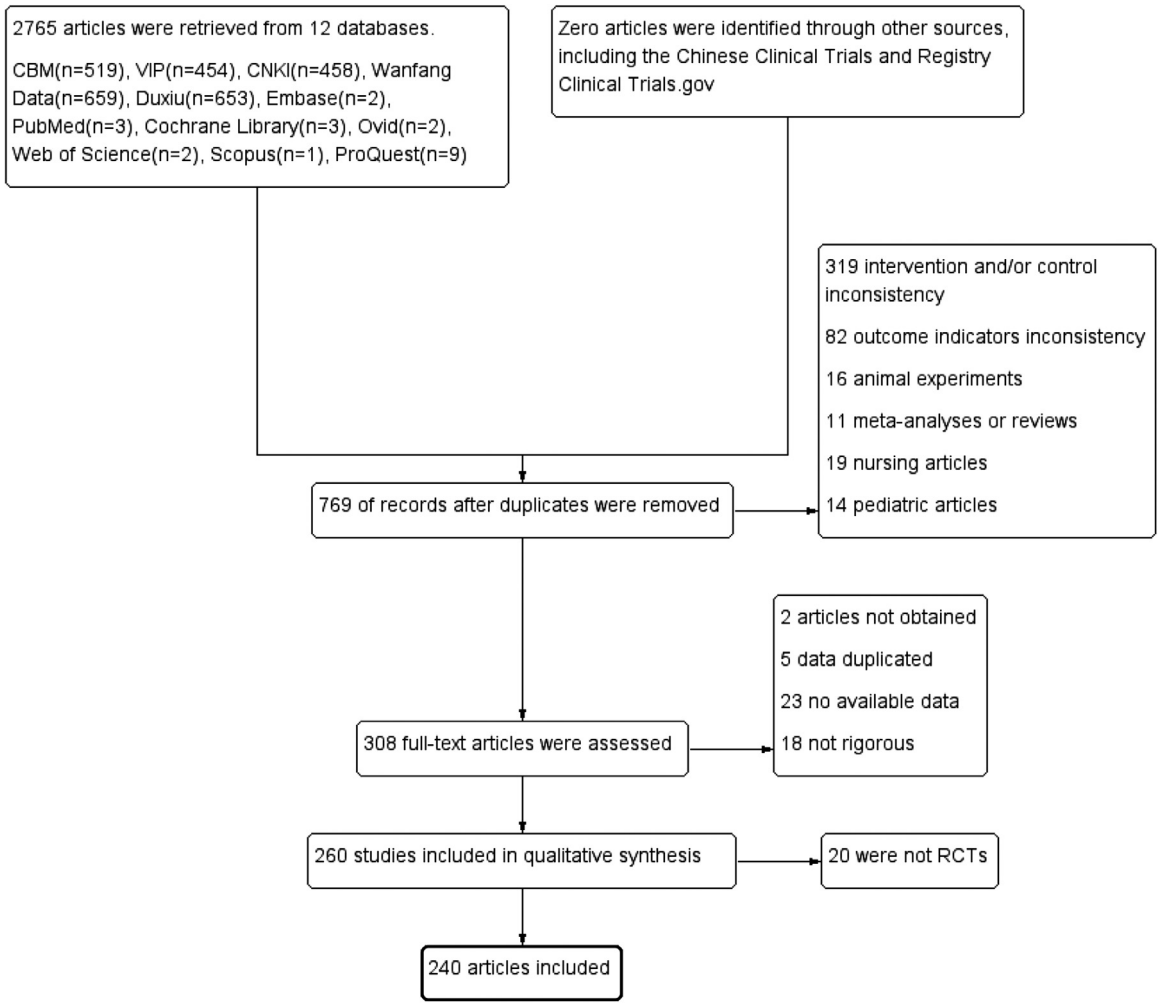

Figure 1. Literature screening flow chart.

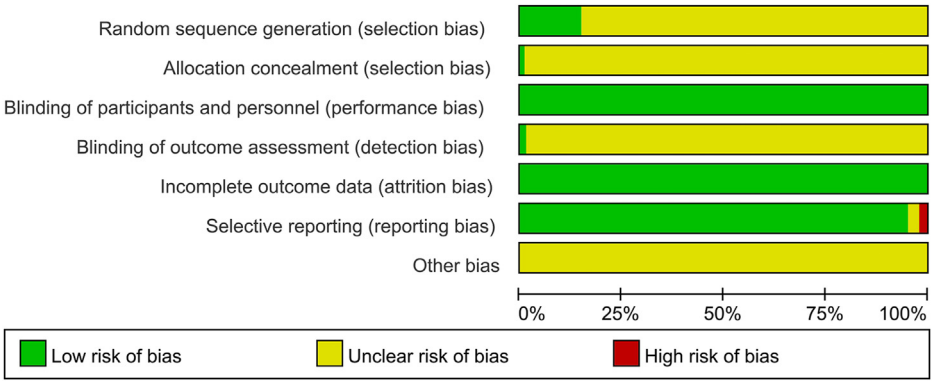

Figure 2. Quality assessment of included studies.

The overall incidence rate of complications

The overall incidence rate of complications was the sum of all kinds of complications in the studies, as shown in Supplementary Table 3. A total of 18 studies reported the overall incidence rate of complications: I^2=47.7%, which suggested that heterogeneity was moderate; hence, we used the fixed effect model. The results suggested that the PHC group could greatly reduce the overall incidence rate of complications (RR=0.35, 95% CI: 0.28–0.43, P <0.001, Supplementary Figure 2). The P-value of Egger's test was <0.05, which showed publication bias. The correction result of the trim and fill method was not very different from the previous results, showing that the result was robust (RR=0.51, 95% CI: 0.30–0.71, P <0.001).

The incidence of delayed polyneuropathy

Only 5 studies reported the incidence of delayed polyneuropathy: I^2=0.0% indicated no heterogeneity, and so we used the fixed effect model. The result indicated that the incidence

Table 1
The summary of outcomes.

Number	Outcomes	Number of studies	RR	WMD	SMD	95% CI	I^2	*P*-value
1	Mortality rate	76	0.20	NA	NA	0.16, 0.25	0.0%	<0.001
2	Hospitalization time (days)	145	NA	−3.89	NA	−4.37, −3.41	98.1%	<0.001
3	The overall incidence rate of complications	18	0.35	NA	NA	0.28, 0.43	47.7%	<0.001
4	Incidence of delayed polyneuropathy	5	0.28	NA	NA	0.13, 0.59	0.0%	0.001
5	Incidence of intermediate syndrome	24	0.23	NA	NA	0.17, 0.31	0.0%	<0.001
6	Incidence of rebound	45	0.15	NA	NA	0.11, 0.20	0.0%	<0.001
7	Incidence of respiratory failure	9	0.29	NA	NA	0.19, 0.44	0.0%	<0.001
8	The overall incidence of adverse reactions	44	0.19	NA	NA	0.17, 0.22	39.0%	<0.001
9	Incidence of blurred vision	32	0.27	NA	NA	0.23, 0.32	44.0%	<0.001
10	Incidence of thirst	7	0.65	NA	NA	0.54, 0.79	54.6%	<0.001
11	Incidence of urinary retention	37	0.20	NA	NA	0.16, 0.24	45.0%	<0.001
12	Incidence of tachycardia	54	0.17	NA	NA	0.14, 0.20	52.4%	<0.001
13	Incidence of fever	20	0.20	NA	NA	0.15, 0.28	0.0%	<0.001
14	Incidence of restlessness	36	0.26	NA	NA	0.22, 0.29	1.3%	<0.001
15	Incidence of disturbance of consciousness	12	0.27	NA	NA	0.21, 0.34	31.9%	<0.001
16	The total symptom disappearance time	94	NA	NA	−2.13	−2.35, −1.90	94.0%	<0.001
17	Disappearance time of muscarinic symptoms	23	NA	NA	−1.92	−2.35, −1.50	93.2%	<0.001
18	Disappearance time of nicotinic symptoms (hours)	10	NA	−3.74	NA	−4.74, −2.74	97.9%	<0.001
19	Disappearance time of central nervous system symptoms (hours)	9	NA	−6.71	NA	−9.18, −4.23	96.7%	0.001
20	Time for cholinesterase activity to return to normal value 50–60%	112	NA	NA	−1.87	−2.03, −1.70	91.4%	<0.001
21	Coma time (hours)	17	NA	−5.57	NA	−7.20, −3.95	98.1%	<0.001
22	Mechanical ventilation time (days)	12	NA	−2.16	NA	−2.79, −1.53	97.6%	<0.001

CI: Confidence intervals; NA: Not applicable; RR: Risk ratios; SMD: Standard mean difference; WMD: Weighted mean difference.

of delayed polyneuropathy was significantly reduced in the PHC group (RR=0.28, 95% CI: 0.13–0.59, *P*=0.001, Supplementary Figure 3).

The incidence of intermediate syndrome

Twenty-four studies reported the incidence of intermediate syndrome. As I^2=0.0%, we used the fixed effect model. The result showed the incidence of intermediate syndrome was greatly reduced in the PHC group (RR=0.23, 95% CI: 0.17–0.31, *P* <0.001, Supplementary Figure 4).

The incidence of rebound

In all, 45 studies reported the incidence of rebound. As I^2=0.0%, we used the fixed effect model. The result showed the incidence of rebound was distinctly reduced in the PHC group (RR=0.15, 95% CI: 0.11–0.20, *P* < 0.001, Supplementary Figure 5).

The incidence of respiratory failure

Only 9 studies reported the incidence of respiratory failure. As I^2=0.0%, we used the fixed effect model. The result suggested that the incidence of respiratory failure was greatly reduced in the PHC group (RR=0.29, 95% CI: 0.19–0.44, *P* <0.001, Supplementary Figure 6).

The overall incidence of adverse reactions

The overall incidence of adverse reactions was the sum of all kinds of adverse reactions in the studies, as shown in Supplementary Table 4. In all, 44 studies reported the overall incidence of adverse reactions. As I^2=39.0%, we used the fixed effect model. The result indicated that the overall incidence of adverse reactions was significantly reduced in the PHC group (RR=0.19, 95% CI: 0.17–0.22, *P* <0.001, Supplementary Figure 7). The *P*-value of Egger's test was 0.037, which indicated publication bias. The correction result of the trim and fill method was not very different from the previous result, indicating that the result was robust (RR = 0.27, 95% CI: 0.12–0.41, and *P* < 0.001).

The incidence of blurred vision

Thirty-two studies reported the incidence of blurred vision. As I^2=44.0%, we used the fixed effect model. The result showed that the incidence of blurred vision was significantly reduced in the PHC group (RR=0.27, 95% CI: 0.23–0.32, *P* <0.001, Supplementary Figure 8).

The incidence of thirst

Only 7 studies reported the incidence of thirst. As I^2=54.6%, which indicated large heterogeneity, we used the random effect model. The result showed that the incidence of thirst was greatly reduced in the PHC group (RR=0.65, 95% CI: 0.54–0.79, *P* <0.001, Supplementary Figure 9).

The incidence of urinary retention

A total of 37 studies reported the incidence of urinary retention. As I^2=45.0%, we used the fixed effect model. The result suggested that the incidence of urinary retention was distinctly reduced in the PHC group (RR=0.20, 95% CI: 0.16–0.24, *P* <0.001, Supplementary Figure 10).

The incidence of tachycardia

A total of 54 studies reported the incidence of tachycardia. As I^2=52.4%, we used the random effect model. The result indicated that the incidence of tachycardia was greatly reduced in the PHC group (RR=0.17, 95% CI: 0.14–0.20, *P* <0.001, Supplementary Figure 11).

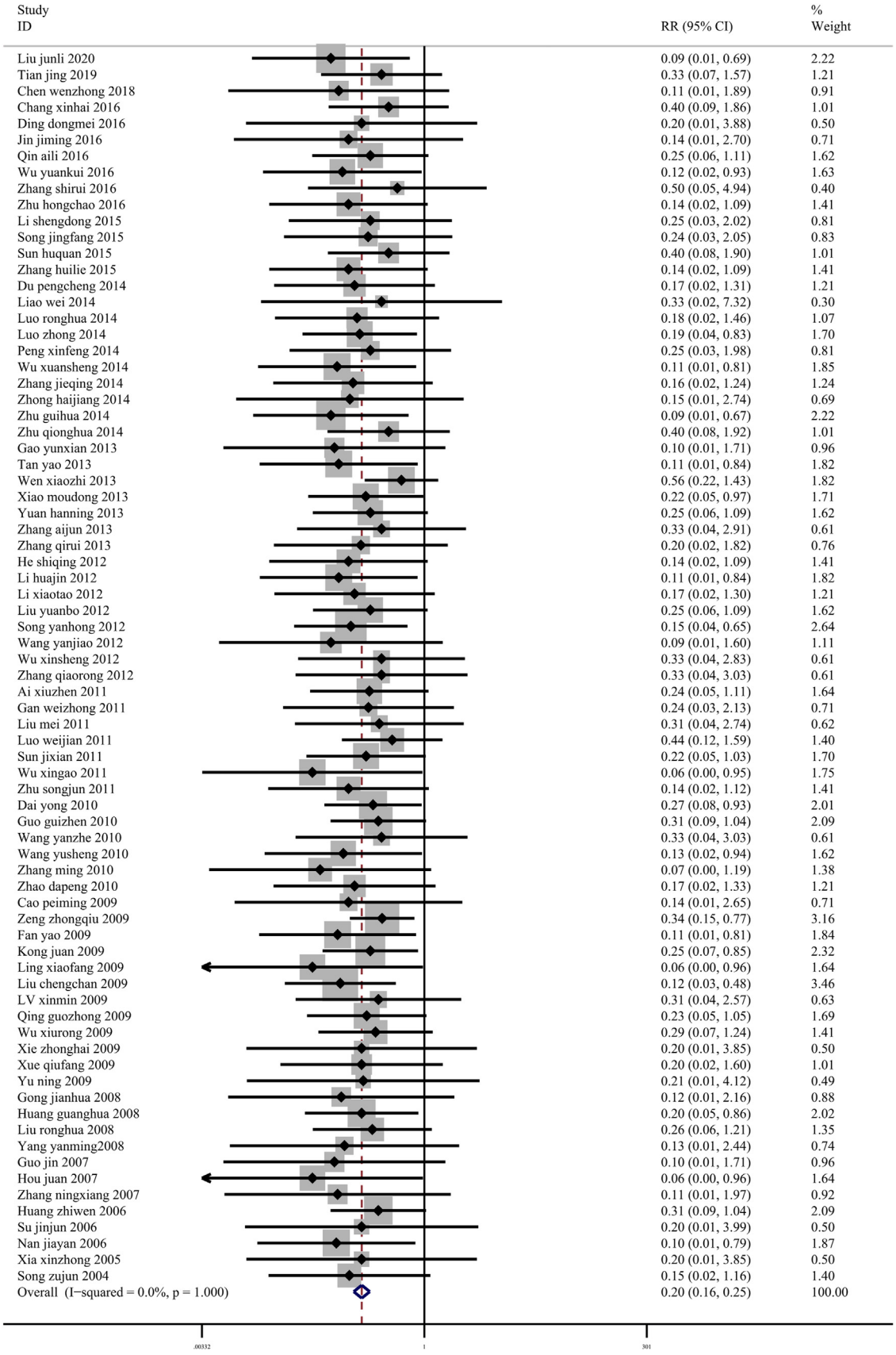

Figure 3. Forest plot of mortality rate. CI: Confidence intervals; RR: Risk ratios.

The incidence of fever

Twenty studies reported the incidence of fever. As I^2=0.0%, we used the fixed effect model. The result suggested that the incidence of fever was distinctly reduced in the PHC group(RR=0.20, 95% CI: 0.15–0.28, P<0.001, Supplementary Figure 12]).

The incidence of restlessness

A total of 36 studies reported the incidence of restlessness. As I^2=1.3%, we used the fixed effect model. The result showed that the incidence of restlessness was significantly reduced in the PHC group (RR = 0.26, 95% CI: 0.22–0.29, and P <0.001, Supplementary Figure 13).

The incidence of disturbance of consciousness

Only 12 studies reported the incidence of disturbance of consciousness. As I^2=31.9%, we used the fixed effect model. The result suggested that the incidence of disturbance of consciousness was distinctly reduced in the PHC group (RR=0.27, 95% CI: 0.21–0.34, P <0.001, Supplementary Figure 14).

The total symptom disappearance time

The total symptom disappearance time refers to the time when all symptoms of the patient have disappeared, including muscarinic, nicotine, and central nervous system symptoms. A total of 94 studies reported the total symptom disappearance time. The time units of nine studies were days, of 10 studies were minutes, and the rest were hours. Here, we use SMD to calculate effect size. As I^2=94.0%, which indicated large heterogeneity, we used the random effect model. The result indicated that the total symptom disappearance time was significantly reduced in the PHC group (SMD = −2.13, 95% CI: −2.35 to −1.90, P < 0.001, Supplementary Figure 15). The P-value of Egger's test was <0.05, which indicated publication bias. The correction result of the trim and fill method was not very different from the previous results, suggesting that the result was robust (SMD= −2.57, 95% CI: −2.83 to −2.30, P <0.001).

The disappearance time of muscarinic symptoms

Twenty-three studies reported the disappearance time of muscarinic symptoms, including 18 studies in hours and 5 studies in days. SMD was used to calculate effect size. Because I^2=93.2%, the random effects model was used. The result indicated that the disappearance time of muscarinic symptoms was distinctly reduced in the PHC group apparently(SMD= −1.92, 95% CI: −2.35 to −1.50, P <0.001, Supplementary Figure 16).

The disappearance time of nicotinic symptoms

Only 10 studies reported the disappearance time of nicotinic symptoms, all in hours. As I^2=97.9%, we used the random effect model. The result showed that the disappearance time of nicotinic symptoms was greatly reduced in the PHC group (WMD = −3.74, 95% CI: −4.74 to −2.74, P <0.001, Supplementary Figure 17).

The disappearance time of central nervous system symptoms

Only 9 studies reported the disappearance time of central nervous system symptoms, all in hours. As I^2=96.7%, we used the random effect model. The result suggested that the disappearance time of central nervous system symptoms was distinctly reduced in the PHC group (WMD= −6.71, 95% CI: −9.18 to −4.23, P=0.001, Supplementary Figure 18).

Time for cholinesterase activity to return to normal value 50–60%

In all, 112 studies included the time for cholinesterase activity to return to normal value 50–60%. The time units of 25 studies were days, of 2 studies were minutes, and the rest were hours. We used SMD to calculate effect size. As I^2=91.4%, we used the random effect model. The result indicated that the time for cholinesterase activity to return to normal value 50–60% was significantly reduced in the PHC group (SMD = −1.87, 95% CI: −2.03 to −1.70, P < 0.001, Supplementary Figure 19). The P-value of Egger's test was <0.05, which showed publication bias. The correction result of the trim and fill method was not very different from the previous results, which meant that the impact of publication bias was small and the result was robust (SMD= −2.06, 95% CI: −2.25 to −1.88, P <0.001).

Coma time

Seventeen studies reported coma time, only 1 in minutes and the others in hours. We converted the study into hours and then performed statistical calculations. As I^2=98.1%, we used the random effect model. The result showed that the coma time was distinctly reduced in the PHC group (WMD= −5.57, 95% CI: −7.20 to −3.95, P <0.001, Supplementary Figure 20). The P-value of Egger's test was 0.041, which indicated publication bias. The correction result of the trim and fill method was not very different from the previous results, showing that the result was robust (WMD= −6.61, 95% CI: −8.75 to −4.47, P < 0.001).

Mechanical ventilation time

Only 12 studies reported the mechanical ventilation time, of which 2 were in hours, and the others in days. We converted the 2 studies in hours into days and analyzed them together with other studies. As I^2=97.6%, we used the random effect model. The result showed that the mechanical ventilation time was distinctly reduced in the PHC group (WMD= −2.16, 95% CI: −2.79 to −1.53, P < 0.001, Supplementary Figure 21). The P-value of Egger's test was 0.350, and so there was no publication bias.

Discussion

Our meta-analysis included 20,797 subjects from 240 studies in 242 different hospitals across China. The results showed that as an anticholinergic drug for AOPP, PHC has many advantages over atropine. First, the PHC group showed decreased mortality rate, and reduced hospitalization time, incidence of various complications, and incidence of various adverse reactions. Moreover, it was also associated with reduced time for disappearance of the three main symptoms of AOPP. Finally,

the time for cholinesterase activity to return to normal value 50–60%, coma time, and mechanical ventilation time were also reduced with PHC treatment.

In the human body, the M_1 receptor is mainly distributed in the central ganglion, while the M_3 receptor is mainly distributed in smooth muscles and glands, and PHC can selectively act on them. The drug can also act on N_1 and N_2 receptors, cross the blood–brain barrier, and play a strong central and peripheral anticholinergic role.[273] The absorption rate of PHC in the body is very fast. After 2 min, PHC could be detected in the blood of all subjects, and the blood concentration reaches a peak in 20–30 min.[274] In the use of anticholinergic drugs in AOPP, choosing PHC instead of atropine can better, faster, and more comprehensively control the symptoms of central nervous system poisoning and a series of poisoning symptoms such as increased secretions of the gastrointestinal tract, respiratory tract, and glands.[273]

AOPP can cause cardiac damage and hemodynamic abnormalities by causing cellular hypoxia, interfering with myocardial cell membrane ion channels and inflammation.[42] The M_2 receptor is the main subtype of M receptor in the heart. PHC has no obvious selectivity for M_2 receptor, and so it has little effect on heart rate. When the heart rate is abnormal (usually bradycardia) caused by AOPP, PHC can regulate the heart rate bidirectionally through the post-cardiac sympathetic nervous system and the M_1 and M_3 receptors in the cardiovascular center, so that the heart rate gradually returns to normal, while atropine often causes tachycardia and increased myocardial oxygen consumption [275,276]. In an AOPP test for mice, in terms of morphology, light microscopy and electron microscopy indicated that the degree of myocardial damage in the PHC group was significantly mild. At the same time, the creatine kinase in the PHC group was also lower.[276]

OP and their metabolites can directly damage hepatocytes, cause hepatocyte edema, degeneration and necrosis, and inhibit liver microsomal enzymes. Some patients may have different degrees of abnormal liver function and may have acute explosive liver failure.[42] An experiment on rats showed that lysosomal release can be reduced by PHC and lipid peroxidation can be inhibited by PHC, and it can also improve microcirculation to inhibit liver inflammation.[277]

Patients with AOPP often have convulsions that cause changes in electroencephalogram (EEG). Another experiment on rats showed that atropine could only partially resist the EEG changes caused by AOPP, while PHC could completely resist the EEG changes and reduce the number of convulsions, which was significantly better than atropine.[278]

Some studies suggested that oxidative stress promotes the pathophysiological process of AOPP.[279–281] Two studies have proved that pretreatment with PHC can reduce myocardial injury in cardiac ischemia-reperfusion injury, and reduce lung histopathological changes, inhibit pulmonary edema, reduce cytokine release and oxidative stress, and inhibit lung cell apoptosis in acute lung injury caused by pulmonary artery ischemia-reperfusion, to improve lung function [282,283].

The studies included in our meta-analysis span >20 years. More than 20,000 subjects in the 240 included studies were from 242 different hospitals across 29 provinces, municipalities, and autonomous regions in China. Our sample size was larger and the outcomes were more comprehensive than the meta-analyses [39–41] published in 2010–2012 in Chinese.

Our meta-analysis has some limitations. The methodological quality of the studies varied. In random methods, allocation concealment, and blinding of outcome assessment, the quality of most articles was evaluated as unclear, and there was selective reporting for individual articles. All studies were conducted in mainland China, which may have led to sampling bias. Despite a comprehensive search of the database, no gray literature was found. Some outcomes were highly heterogeneous. The heterogeneity between these studies may have affected the validity of the meta-analysis. Nevertheless, this meta-analysis did identify a series of advantages of PHC in the treatment of AOPP. We recommend that PHC be the first choice in clinical treatment as the anticholinergic drug of choice in AOPP, as it appears to have more clinical benefits than atropine.

Conclusions

Our study suggested that PHC has a series of advantages over atropine as an anticholinergic drug in AOPP. In future, we need more high-quality research to prove our conclusion.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2022.07.006.

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