Original Article

Role of penehyclidine in acute organophosphorus pesticide poisoning

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BACKGROUND: Penehyclidine is a newly developed anticholinergic agent. We aimed to investigate the role of penehyclidine in acute organophosphorus pesticide poisoning (OP) patients.

METHODS: We searched the Pubmed, Cochrane library, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical literature (CBM) and Wanfang databases. Randomized controlled trials (RCTs) recruiting acute OP patients were identified for meta-analysis. Main outcomes included cure rate, mortality rate, time to atropinization, time to 60% normal acetylcholinesterase (AchE) level, rate of intermediate syndrome (IMS) and rate of adverse drug reactions (ADR).

RESULTS: Sixteen RCTs involving 1,334 patients were identified. Compared with the atropine- or penehyclidine-alone groups, atropine combined with penehyclidine significantly increased the cure rate (penehyclidine+atropine vs. atropine, 0.97 vs. 0.86, *RR* 1.13, 95% *CI* [1.07–1.19]; penehyclidine+atropine vs. penehyclidine, 0.93 vs. 0.80, *RR* 1.08, 95% *CI* [1.01–1.15]) and reduced the mortality rate (penehyclidine+atropine vs. atropine, 0.015 vs. 0.11, *RR* 0.17, 95% *CI* [0.06–0.49]; penehyclidine+atropine vs. penehyclidine, 0.13 vs. 0.08, *RR* 0.23, 95% *CI* [0.04–1.28]). Atropine combined with penehyclidine in OP patients also helped reduce the time to atropinization and AchE recovery, the rate of IMS and the rate of ADR. Compared with a single dose of atropine, a single dose of penehyclidine also significantly elevated the cure rate, reduced times to atropinization, AchE recovery, and rate of IMS.

CONCLUSION: Atropine combined with penehyclidine benefits OP patients by enhancing the cure rate, mortality rate, time to atropinization, AchE recovery, IMS rate, total ADR and duration of hospitalization. Penehyclidine combined with atropine is likely a better initial therapy for OP patients than atropine alone.

KEY WORDS: Penehyclidine; Organophosphorus pesticide poisoning; Meta-analysis

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INTRODUCTION

Acute severe organophosphorus pesticide (OP) poisoning, which is defined as cholinesterase activity less than 30% in a patient presenting with an acute onset M- and N-cholinergic receptor activation syndrome, is a common type of accidental or suicidal pesticide poisoning in developing countries,[1] especially in rural China.[2,3] Although the mortality rate for OP poisonings

in China has dropped over the past several years, OP poisoning still accounts for more than half of all intoxication cases in emergency departments throughout China and leads to more than 80% of total poisoning deaths.[2,4,5]

Anticholinergic agents are the cornerstone of therapy for relieving symptoms in OP patients, especially pulmonary edema. Atropine is the most commonly used anticholinergic antidote for treating cholinergic syndrome, especially in OP patients.[2,3,6] However, its M-receptor blockade ability sometimes leads to adverse effects on intoxicated patients, particularly concerning vital signs (e.g., elevated heart rate and blood pressure). In the initial phase of treating an OP poisoning patient in the emergency department, the proper initial dose of atropine is hard to judge and may lead to severe complications.[7-9] The dose of atropine administration does vary a lot between different medical centers and managing the effect of atropine is challenging.[10] The adverse effects of atropine are another cause of poor prognosis or even death in OP patients.[6,11]

Penehyclidine is a relatively new anticholinergic agent developed by the Chinese Academy of Military Medical Sciences targeting mainly M1 and M3 cholinergic receptors.[12] After intramuscular injection of 1 mg of penehyclidine hydrochloride in healthy adults, penehyclidine hydrochloride can be detected in the bloodstream in two minutes. The peak plasma concentration (13.20 μg/L) occurs in about 30 minutes, and the elimination half-life is 10.35 hours. Due to penehyclidine's high-selectivity for M-receptors, it relieves the symptoms associated with M-receptor activation in OP patients and also reduces some of the adverse effects of atropine caused by its M-receptor blockade mechanism, such as fever and bradycardia. However, the time to atropinization is possibly prolonged due to the selectivity of penehyclidine as compared to the general cholinergic receptor-blocking ability of atropine, and penehyclidine needs longer period of time to reach functional volume in the blood as compared to atropine (almost 1 hour vs. 4–8 minutes).[13,14]

Clinical observations showed that atropine combined with penehyclidine is a potentially effective therapy for OP poisoning patients, reducing the rate of adverse drug reactions (ADR) of atropine and improving overall prognosis.[3,10,15,16] Nevertheless, despite the affordable price for people in developing countries and wide usage of penehyclidine, it has not yet been clearly recommended in any guideline or consensus worldwide. A published meta-analysis of clinical trials between 2000 and 2010 concluded that the administration of penehyclidine compared to atropine for severe OP poisoning patients could increase the cure rate and reduce adverse effects significantly and recommended that atropine combined with penehyclidine may also be beneficial for OP poisoning patients.[17] However, the quality of included articles was relatively low and there have since been few published guidelines advocating for atropine combined with penehyclidine as a standard treatment for OP patients. We aimed to synthesize the most recent publications and evaluate the effects of penehyclidine alone or combined with atropine toward OP poisoning patients.

METHODS

Search strategy

Our research team searched the following databases: Pubmed, Cochrane library, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical literature (CBM) and Wanfang. English search terms included organophosphate poisoning (MeSH term), organophosphorus, organophosphorus poisoning, OP poisoning, OP, atropine, and penehyclidine. Chinese search terms were also included, consisting of words with the same meaning as the aforementioned English terms, including (in pinyin romanization): "a tuo pin", "wu yi kui mi", "you ji lin", "chang tuo ning" and "zhong du". Afterwards, two members of our research team cross-checked all reference lists independently for agreement.

Inclusion and exclusion criteria

Articles were included if they met all of the following criteria: (i) randomized controlled trial (RCT); (ii) study population included accidental or suicidal acute OP patients; (iii) study included comparisons at least between atropine combined with penehyclidine group, a penehyclidine group and an atropine group; (iv) one or more of the following indexes were reported in the article: cure rate, mortality rate, time to atropinization, time to 60% normal acetylcholinesterase (AchE) level, rate of intermediate syndrome (IMS), and rate of ADR.

Articles were excluded for the following reasons: (i) language other than Chinese or English; (ii) study not carried out on human beings; (iii) data was unavailable or unextractable; (iv) important outcomes (cure rate or mortality rate) were not reported; (v) study was performed primarily on special populations (e.g., patients with HIV or tuberculosis); (vi) study consisted of

patients who were not initially treated with penehyclidine or penehyclidine combined with atropine; (vii) study was a review article or case report.

Quality assessment

Two reviewers independently evaluated the included studies under the guide of the Cochrane Collaboration's quality assessment tool. First, they excluded duplicate articles and then performed title and abstract screening. Second, they screened the full-text articles for inclusion or exclusion. If there was a controversial decision, a third reviewer from our team was consulted as a tie-breaker. The following seven aspects were evaluated, including allocation concealment, blinding of participants and personnel, blinding of outcome assessment, random sequence generation, incomplete outcome data, selective reporting and other sources of bias. The results were stratified as low risk of bias, high risk of bias and unclear risk of bias.

Statistics

Two researchers independently extracted and evaluated the data of baseline characteristics using Excel 2016 (Microsoft Corporation, Redmond, USA). The main outcomes were cure rate (defined as all clinical syndromes attenuated and vital signs returned to be normal), mortality rate, time to atropinization (which was defined as first the occurrence of any of the following findings: dry skin, dilated pupils, reduced levels of abnormal breath sounds, and a heart rate beyond 120 bpm), time to 60% normal AchE level, rate of IMS, rate of ADR and duration of hospitalization. The estimated risk ratio (*RR*), standardized mean difference (SMD) and 95% confidence intervals (95% *CI*) were pooled using Review Manager 5.3 (Cochrane Collaboration, UK). A *P*-value less than 0.05 was defined as statistically significant. Heterogeneity level was evaluated using I^2. An $I^2 > 50\%$ suggested high heterogeneity among studies and a randomized model was used to pool the data, while a fixed model was used if I^2 was no more than 50%. Funnel plots were used to demonstrate reporting bias.

RESULTS

Studies included

Our study found 3,918 articles in the first screening stage, 154 of these articles came from PubMed, 98 from EMBASE, 0 from the Cochrane library, 1,878 from CNKI, 1,005 from CBM and 783 from Wanfang. After secondary abstraction and full-text screening by our reviewers, 16 articles (all from the CNKI database) were identified, recruiting 1,334 patients in total.[2,4,10,11,13,14,18-27] The screening procedure is illustrated in Figure 1. All included studies were RCTs published in Chinese. Details of the articles included are shown in Table 1.

Baseline characteristics

Sixteen RCTs enrolled 1,334 OP patients in total. There were 388 patients in the penehyclidine+atropine group, 378 patients in the penehyclidine-only group and 568 patients in the atropine-only group. The mean age was 35.1±6.2 in the penehyclidine+atropine group, 38.8±2.3 in the penehyclidine-only group and 34.2±11.0 in the atropine-only group (*P*=0.556). The ingestion amount was 90.7±26.1 mL in the penehyclidine+atropine group, 62.9±28.1 mL in the penehyclidine-only group and 76.0±30.3 mL in the atropine-only group (*P*=0.521). The AchE level was 159.3±41.4 U/L in the penehyclidine+atropine group,158.2±118.7 U/L in the penehyclidine-only group and 168.2±103.1 U/L in the atropine-only group (*P*=0.212). All enrolled studies gave their patients a standardized amount of oxime.

Evaluation of bias

The methodological quality of included studies was assessed under the guidelines of the Cochrane Collaboration's tool. All 16 studies included mentioned a randomization procedure and reported the process of random sequence generation, however, no included studies reported details regarding allocation concealment. There was also a high risk of bias concerning both participants and personnel as well as outcome assessment. The reasons for missing data between groups are similar in the recruited studies. There was a low risk of bias regarding selective reporting. Thirteen studies met criteria of low risk

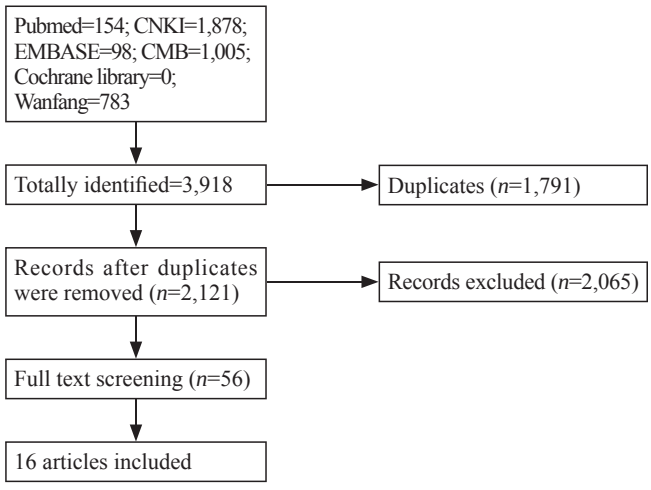


Figure 1. Flow diagram.

Table 1. Included articles

First author	Journal	Organophosphate component	N	Drug administration
Lin et al[2] 2016	Chinese Journal of Modern Drug Application	Not reported	150	Penehyclidine+atropine group, atropine 10–20 mg IV and penehyclidine 1 mg IM three times a day, then atropine 5–10 mg every 5–10 minutes until atropinization; penehyclidine group, penehyclidine 4–6 mg IM then penehyclidine 2–3 mg every 1–2 hours until atropinization; atropine group, atropine 10–20 mg IV then 5–10 mg IV every 5–10 minutes until atropinization
Wu et al[4] 2016	Heilongjiang Medical Journal	Not reported	83	Penehyclidine group, penehyclidine 4–6 mg IV initially; atropine group, atropine 10–20 mg IV initially
Fu et al[10] 2015	11th National Conference on Disaster Medicine with Integrated Traditional Chinese Medicine and Western Medicine	Not reported	62	Penehyclidine group, penehyclidine 4–6 mg IM initially then 1–2 mg until atropinization; atropine group, atropine 20–40 mg IV initially
Zhao et al[11] 2015	World Notes	Not reported	48	Penehyclidine+atropine group, penehyclidine 4–6 mg IM initially, atropine 1–2 mg every 8–12 hours; atropine group, atropine 10–20 mg IM every 1 hour until atropinization
Liang et al[13] 2014	Contemporary Medicine	Not reported	120	Penehyclidine+atropine group, atropine 10–20 mg IV initially then 5–10 mg every 5–10 minutes until atropinization, then Penehyclidine 1–2 mg IM every 8–12 hours; atropine group, atropine 10–20 mg IV initially then 5–10 mg every 5–10 minutes until atropinization
Sun et al[14] 2012	China Modern Medicine	Not reported	58	Penehyclidine+atropine group, penehyclidine 4–5 mg IM+atropine 10–20 mg IV initially; atropine group, atropine 10–20 mg IV then additional atropine every 10–30 minutes until atropinization
Zeng et al[18] 2011	Fujian Medicine Journal	Not reported	62	Penehyclidine group, penehyclidine 4–6 mg IM initially; atropine group, atropine 3–5 mg IV then 5–15 mg every 5–10 minutes until atropinization
Liu et al[19] 2012	Medical Innovation of China	Dichlorvos, omethoate, rogor, methamidophos, dipterex	64	Penehyclidine group, penehyclidine 5 mg IV, then 3 mg every 30–60 minutes until atropinization; atropine group, atropine 10 mg IV initially
Chen et al[20] 2011	Guide of China Medicine	Cynamid, alkron, demeton, methamidophos, rogor	80	Penehyclidine+atropine group, penehyclidine 1 mg IM+atropine 10–20 mg IV, then atropine 10 mg every 10–15 minutes until atropinization
Guan et al[21] 2015	World Latest Medicine Information	Not reported	60	Penehyclidine+atropine group, penehyclidine 4–6 mg IM initially, then atropine IV until atropinization; atropine group, atropine 10–15 mg IV every 10–30 minutes until atropinization
Wang et al[22] 2010	Chinese Journal of Modern Drug Application	Cynamid, alkron, methamidophos, dichlorvos, rogor, azodrin, phoxime	76	Penehyclidine+atropin group, penehyclidine 2–3 mg IM +atropine 5–10 mg IV, then 5–10 mg atropine every 5–10 minutes until atropinization; penehyclidine group, 4 mg IM, additional drug due to patients condition until atropinization; atropine group, 5–10 mg atropine IV, then 5–10 mg atropine every 5–10 minutes until atropinization
Yi et al[23] 2010	Journal of Lingnan Emergency Medicine	Dichlorvos, methamidophos, acephate, alkron, malathion	102	Penehyclidine+atropin group, atropine 10 mg intravenously (IV) + penehyclidine 5 mg intramuscularly (IM), then 5 mg atropine every 5–10 minutes until atropinization; penehyclidine group, 6 mg penehyclidine IM then 3 mg penehyclidine IM every 30 minutes until atropinization; atropine group, 10 mg atropine IV then 5 mg atropine IV until atropinization
Luo et al[24] 2014	Medicine	Methamidophos, dichlorvos, rogor, dipterex	98	Penehyclidine+atropine group, atropine 10–15 mg IV and penehyclidine 4–6 mg IM, then atropine IV until atropinization; penehyclidine group, penehyclidine 4–6 mg IM initially; atropine group, atropine 10–15 mg IV every 10–30 minutes until atropinization
Shi et al[25] 2012	Journal of Clinical Emergency	Omethoate, dichlorvos, methamidophos	56	Penehyclidine group, penehyclidine 6 mg IV, then 3 mg every 30–60 minutes until atropinization; atropine group, atropine 20 mg IV initially
Zhou et al[26] 2012	Occupation and Health	Dichlorvos, alkron, rogor, methamidophos, cynamid, demeton	180	Penehyclidine+atropine group, penehyclidine 4–6 mg IM+atropine 3–5 mg IV, then atropine 3–5 mg atropine every 3–5 minutes until atropinization; penehyclidine group, penehyclidine 4–6 mg IM, then 2–3 mg after 30–60 minutes, then 1–2 mg until atropinization; atropine group, atropine 5–10 mg IV, then 5–10 mg every 5–10 minutes until atropinization
Liu et al[27] 2011	Modern Journal of Integrated Traditional Chinese and Western Medicine	Not reported	35	Penehyclidine group, penehyclidine 4–6 mg IM initially; atropine group, atropine 10–20 mg IV then 5–15 mg every 15–30 minutes until atropinization

of other bias while one of the studies failed to report baseline characteristics. Therefore, all studies were judged to be of poor methodological quality (Figure 2).

Cure rate

Penehyclidine + atropine vs. atropine alone

Seven studies included eligible data on cure rates between penehyclidine+atropine and atropine-alone groups, including 594 individuals. A fixed model was used due to low heterogeneity in these studies (I^2=49%). Pooled statistics showed that the cure rate was significantly higher in the penehyclidine+atropine group than in the atropine-alone group (0.97 vs. 0.86, *RR* 1.13, 95% *CI* 1.07–1.19, *P*<0.00001).

Penehyclidine alone vs. atropine alone

Eight studies included eligible data on cure rates between penehyclidine alone and atropine alone groups, including 569 individuals. A fixed model was used due to low heterogeneity in these studies (I^2=48%). Pooled statistics showed that the cure rate was significantly higher in the penehyclidine group than in the atropine group (0.93 vs. 0.80, *RR*=1.16, 95% *CI* 1.08–1.24, *P*<0.00001).

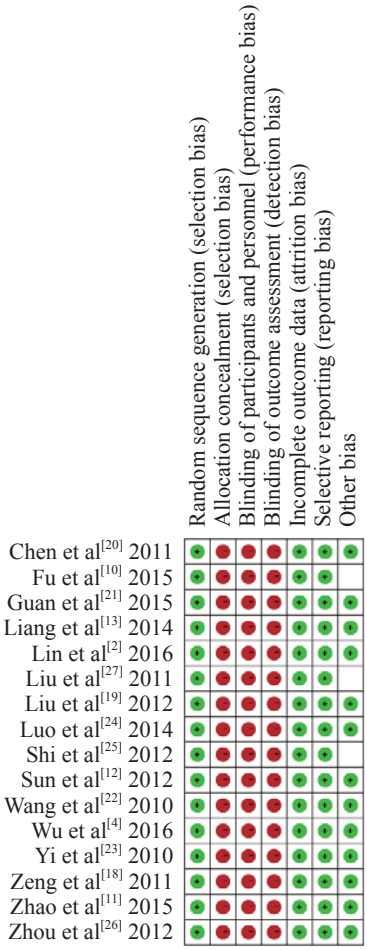


Figure 2. Risk of bias summary.

Penehyclidine+atropine vs. penehyclidine alone

Three studies included eligible data on cure rates between penehyclidine+atropine and penehyclidine-alone groups, including 267 individuals. A fixed model was used due to low heterogeneity in these studies (I^2=0%). Pooled statistics showed that cure rate was significantly higher in the penehyclidine+atropine group than in the penehyclidine-alone group (0.93 vs. 0.80, *RR*=1.08, 95% *CI* 1.01–1.15, *P*=0.02). Forest plots of the comparative cure rates are shown in Figure 3.

Mortality rate

Penehyclidine+atropine vs. atropine alone

Five studies included eligible data on mortality rates between penehyclidine+atropine and atropine-alone groups, including 399 individuals. A fixed model was used because of low heterogeneity in these studies (I^2=0%). Pooled statistics showed that the mortality rate was significantly lower in the penehyclidine+atropine group than in the atropine-alone group (0.015 vs. 0.11, *RR*=0.17, 95% *CI* 0.06–0.49, *P*=0.0009).

Penehyclidine alone vs. atropine alone

Seven studies included eligible data on mortality rates between penehyclidine-alone and atropine-alone groups, including 429 individuals. A fixed model was used due to low heterogeneity in these studies (I^2=0%). Pooled statistics showed that the mortality rate was significantly lower in the penehyclidine-alone group than in the atropine-alone group (0.06 vs. 0.16, *RR*=0.35, 95% *CI* 0.19–0.65, *P*=0.001).

Penehyclidine+atropine vs. penehyclidine alone

Two studies included eligible data on mortality rates between penehyclidine+atropine and penehyclidine-alone groups, including 151 individuals. A fixed model was used because of low heterogeneity in these studies (I^2=0%). Pooled statistics showed that the mortality rate was comparable between the penehyclidin+atropine group and the penehyclidine-alone group (0.013 vs. 0.08, *RR*= 0.23, 95% *CI* 0.04–1.28, *P*=0.09). Forest plots of the comparative mortality rates are shown in Figure 4.

Time to atropinization

Penehyclidine+atropine vs. atropine alone

Seven studies included eligible data on time to atropinization between penehyclidine+atropine and atropine-alone groups, including 546 individuals. A

randomized model was used due to high heterogeneity in these studies (I^2=96%). Pooled statistics showed that the time to atropinization was significantly shorter in the penehyclidine+atropine group than in atropine-alone group (SMD=-1.44, 95% *CI* -2.37– -0.51, *P*<0.00001).

Penehyclidine alone vs. atropine alone

Five studies included eligible data on time to atropinization between penehyclidine-alone and atropine-alone groups, including 344 individuals. A randomized model was used because of high heterogeneity in these studies (I^2=97%). Pooled statistics showed that the time to atropinization was significantly longer in the penehyclidine-alone group than in the atropine-alone group (SMD=1.00, 95% *CI* 0.75–1.26, *P*<0.00001).

Penehyclidine+atropine vs. penehyclidine alone

Four studies included eligible data on time to atropinization between penehyclidine+atropine and penehyclidine-alone groups, including 284 individuals. A randomized model was used because of high heterogeneity in these studies (I^2=97%). Pooled statistics showed that the time to atropinization was significantly shorter in the penehyclidine+atropine group than in the penehyclidine-alone group (SMD=-1.53, 95% *CI* -1.83– -1.24, *P*<0.00001).

Time to 60% normal AchE level

Penehyclidine+atropine vs. atropine alone

Six studies included eligible data on time to 60% normal AchE level between penehyclidine+atropine and atropine-alone groups, including 543 individuals. A randomized model was used due to high heterogeneity in these studies (I^2=90%). Pooled statistics showed that the time to 60% normal AchE level was significantly shorter in the penehyclidine+atropine group than in the atropine-alone group (SMD=-1.69, 95% *CI* -1.89– -1.48, *P*<0.00001).

Penehyclidine alone vs. atropine alone

Five studies included eligible data on time to 60% normal AchE level between penehyclidine-alone and atropine-alone groups, including 411 individuals. A fixed model was used due to low heterogeneity in these studies (I^2=31%). Pooled statistics showed that the time to

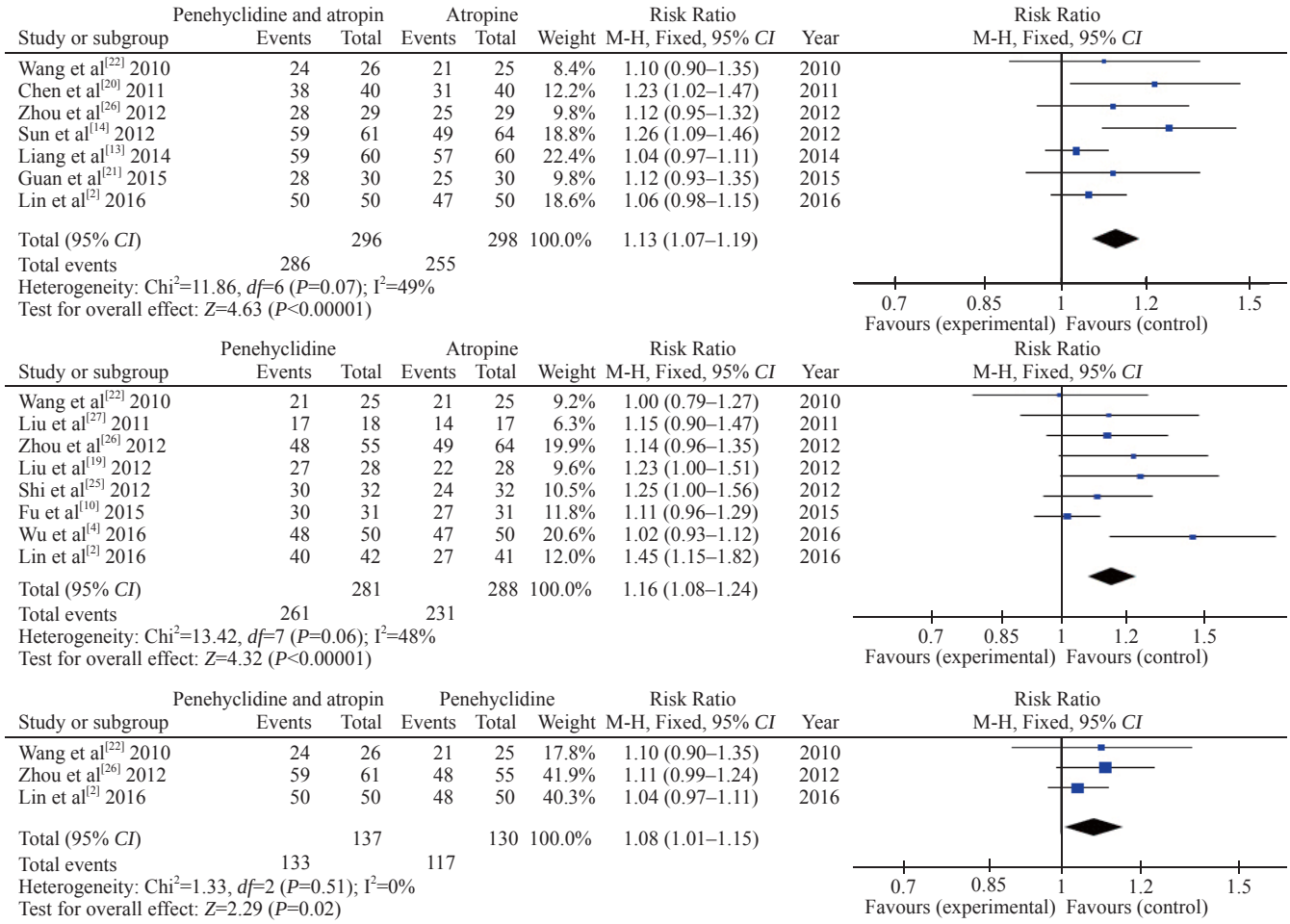


Figure 3. Cured rate.

60% normal AchE level was significantly shorter in the penehyclidine-alone group than in atropine-alone group (SMD=-1.27, 95%*CI* -1.53– -1.01, *P*<0.00001).

Penehyclidine+atropine vs. penehyclidine alone

Three studies included eligible data on time to 60% normal AchE level between penehyclidine+atropine and penehyclidine-alone groups, including 284 individuals. A randomized model was used because of high heterogeneity in these studies (I^2=94%). Pooled statistics showed that the time to 60% normal AchE level was comparable between the penehyclidine+atropine and the penehyclidine-alone groups (SMD=-0.77, 95%*CI* -1.83–0.30, *P*=0.16).

Rate of IMS

Penehyclidine+atropine vs. atropine alone

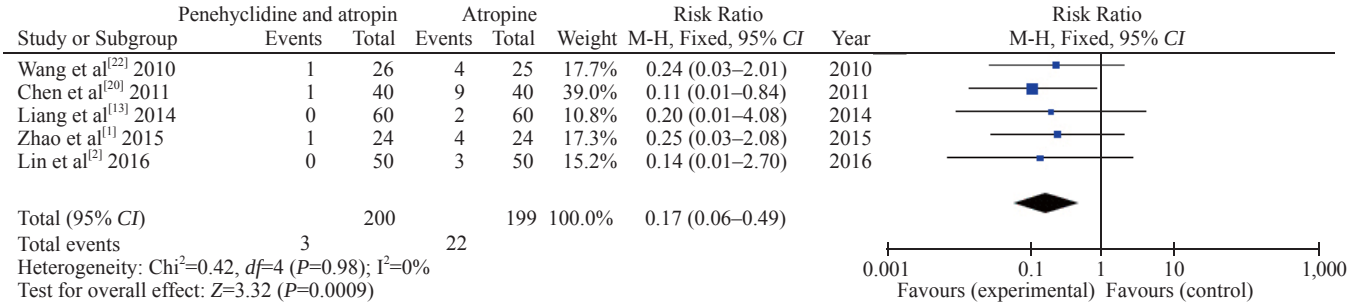
Three studies included eligible data on the rate of IMS between penehyclidine+atropine and atropine-alone groups, including 275 individuals. A fixed model was used due to low heterogeneity in these studies (I^2=0%). Pooled statistics showed that the rate of IMS was significantly lower in the penehyclidine+atropine group than in the atropine-alone group (0.058 vs. 0.20, *RR*=0.31, 95% *CI* 0.15–0.64, *P*=0.002).

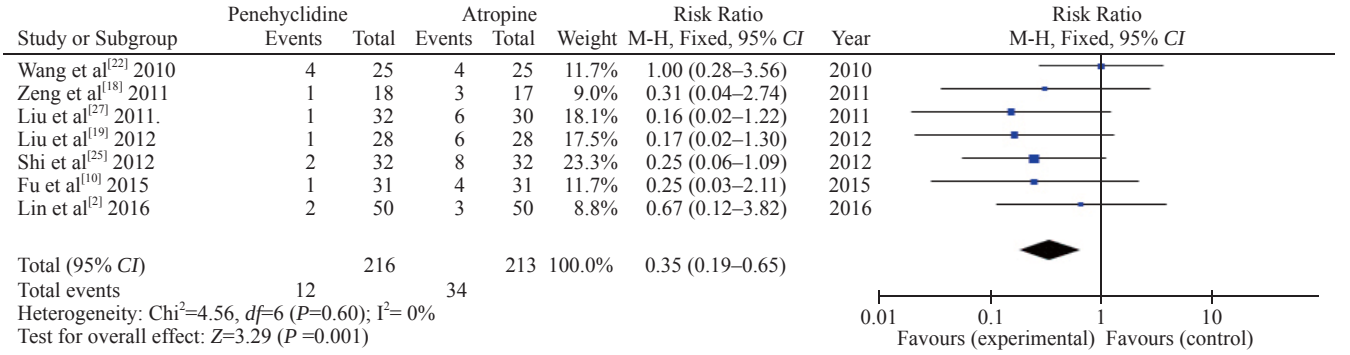
Penehyclidine alone vs. atropine alone

Four studies included eligible data on the rate of IMS between penehyclidine-alone and atropine-alone groups, including 305 individuals. A fixed model was used because of low heterogeneity in these studies (I^2=0%). Pooled statistics showed that the rate of IMS was significantly lower in the penehyclidine-alone group than in the atropine-alone group (0.082 vs. 0.22, *RR*=0.39, 95% *CI* 0.21–0.70, *P*=0.002).

Penehyclidine+atropine vs. penehyclidine alone

Two studies included eligible data on the rate of IMS between penehyclidine+atropine and penehyclidine-alone groups, including 184 individuals. A fixed model was used due to low heterogeneity in these studies (I^2=0%). Pooled statistics showed that the rate of IMS was comparable between the penehyclidine+atropine and the penehyclidine-alone groups (0.072 vs. 0.11, *RR*=0.70, 95% *CI* 0.28–1.78, *P*=0.45).





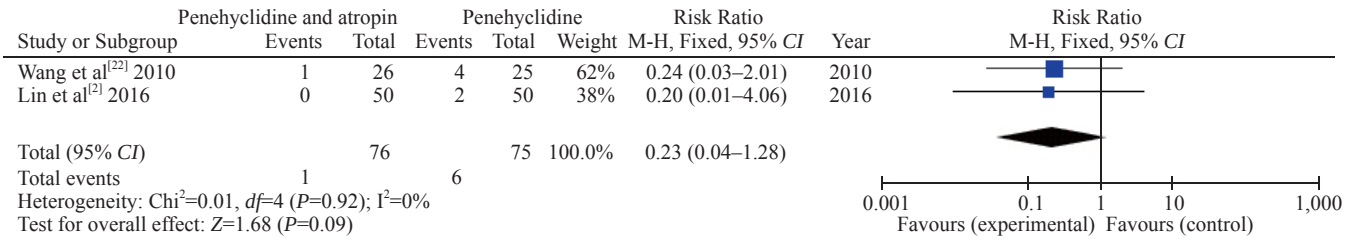


Figure 4. Mortality rate.

Rate of total ADR

Penehyclidine+atropine vs. atropine alone

Four studies included eligible data on the rate of total ADR between penehyclidine+atropine and atropine-alone groups, including 323 individuals. A fixed model was used because of low heterogeneity in these studies (I^2=12%). Pooled statistics showed that the rate of total ADR was significantly lower in the penehyclidine+atropine group than in the atropine-alone group (0.044 vs. 0.24, *RR*=0.19, 95% *CI* 0.09–0.41, *P*<0.0001).

Statistics on the rates of total ADR were not extractable for the penehyclidine-alone vs. atropine-alone groups nor for the penehyclidine+atropine vs. penehyclidine-alone groups.

Duration of hospitalization

Penehyclidine+atropine vs. atropine alone

Seven studies included eligible data on duration of hospitalization between penehyclidine+atropine and atropine-alone groups, including 556 individuals. A randomized model was used because of high heterogeneity in these studies (I^2=77%). Pooled statistics showed that the duration of hospitalization was significantly shorter in the penehyclidine+atropine group than in the atropine-alone group (SMD=-1.35, 95% *CI* -1.74– -0.95, *P*<0.00001).

Penehyclidine alone vs. atropine alone

Three studies included eligible data on duration of hospitalization between penehyclidine-alone and atropine-alone groups, including 247 individuals. A randomized model was used because of high heterogeneity in these studies (I^2=64%). Pooled statistics showed that the duration of hospitalization was comparable between the penehyclidine-alone and atropine-alone groups (SMD=-0.42, 95% *CI* -0.85–0.01, *P*=0.06).

Penehyclidine+atropine vs. penehyclidine alone

Two studies included eligible data on duration of hospitalization between penehyclidine+atropine and penehyclidine-alone groups, including 181 individuals. A randomized model was used due to high heterogeneity in these studies (I^2=97%). Pooled statistics showed that the duration of hospitalization was comparable between the penehyclidine+atropine and penehyclidine-alone groups (SMD=-1.40, 95% *CI* -3.64–0.84, *P*=0.22). Main outcomes are summarized in Table 2.

DISCUSSION

Accidental and suicidal OP poisoning is still a major cause of in-hospital death among all types of pesticide poisonings.[15] Developing countries account for a majority of these patients.[29] Conventional therapy for OP poisoning consists of two major treatments: reactivating the function of AchE and relieving symptoms (i.e. attenuating cholinergic receptor activity) until AchE function recovers. Unfortunately, despite OP poisoning alone being fully capable of causing high mortality rates, atropine in overdose or from its direct adverse effects is also a source of poor outcomes.[9,30]

Penehyclidine is a newly developed anticholinergic agent that selectively targets M1 and M3 receptors, reducing the adverse effects of atropine due to M-receptor blockade. The time to atropinization is prolonged, however, when using penehyclidine.[3,6,17] Thus, many medical centers combine the use of atropine and penehyclidine in order to maintain a balanced outcome of time to atropinization and cure rate.[11,14,29] A retrospective study of two cases of OP poisoning in pregnant women also showed beneficial effects of penehyclidine.[16] Although both fetuses died, the two women both reported no complications and recovered. Despite its reported utility, there is still a lack of high-quality evidence or standardized regimens of penehyclidine combined with atropine for OP poisoning patients.

The mechanism of action of atropine combined with penehyclidine on severe OP poisoning patients is not yet clearly understood. While penehyclidine can relieve the effects of muscarinic activation by competing with accumulated acetylcholine against the M1 and M3 receptors, the faster time to reach 60% normal AchE level we found in this study is not well explained by this

Table 2. Main outcomes

Variables	Penehyclidine and atropine vs. Atropine			Penehyclidine vs. Atropine			Penehyclidine and atropine vs. Penehyclidine		
	RR or SMD	95% *CI*	*P*	*RR* or SMD	95% *CI*	*P*	*RR* or SMD	95% *CI*	*P*
Cured rate	1.13	1.07–1.19	<0.00001	1.16	1.08–1.24	<0.00001	1.08	1.01–1.15	0.02
Mortality rate	0.17	0.06–0.49	0.0009	0.35	0.19–0.65	0.001	0.23	0.04–1.28	0.09
Time to atropinization	-1.44	-2.37– -0.51	0.002	1.00	0.75–1.26	<0.00001	-1.53	-1.53– -1.24	<0.00001
Time of AchE back to 60%	-1.69	-1.89– -1.48	<0.00001	-1.27	-1.53– -1.01	<0.00001	-0.77	-1.83–0.30	0.16
Rate of IMS	0.31	0.15–0.64	0.002	0.39	0.21–0.70	0.002	0.70	0.28–1.78	0.45
Rate of total ADR	0.19	0.09–0.41	<0.00001	-	-	-	-	-	-
Time of hospitalization	-1.35	-1.74– -0.95	<0.00001	-0.42	-0.85–0.01	0.06	-1.40	-3.64–0.84	0.22

mechanism. Future pharmacological investigations into the mechanism(s) of penehyclidine are still needed to explain some findings of this study.

Other effects of penehyclidine on OP-damaged tissue have been observed.[31] Besides the direct cellular injury effect of OP on organs such as the liver and kidneys, auto-immune reaction is another underlying cause of tissue damage in OP patients. Rat models showed protective effects of penehyclidine on cerebral tissue after ischemia and reperfusion injury by reducing the activation of inflammation and down-regulating cell apoptosis after oxidative stress.[32-34] This kind of neural cell damage can also be caused by intoxication and therefore penehyclidine may help modulate cerebral function after OP poisoning, leading to a reduced IMS rate.[35-37] Similarly, some other in vitro studies and animal models also revealed an immune modulation function of penehyclidine, such as attenuating renal ischemia and reperfusion injury as well as enhancing respiratory function in COPD patients.[38,39] These immune modulation mechanisms of penehyclidine are likely also present in OP patients but future research is still needed to confirm.

Compared with the last meta-analysis from 2012,[17] our research integrates more clinical trials concerning acute OP poisoning patients and evaluated more indexes (such as time to atropinization and adverse drug effects). Our study analyzed the most up to date RCTs, focusing on the effects of atropine combined with penehyclidine on OP poisoning patients. Our pooled statistics revealed that compared to atropine alone, penehyclidine combined with atropine significantly increases the cure rate, reduces the mortality rate, time to atropinization, time to 60% normal AchE level, rate of IMS and total ADR. Also, compared to penehyclidine alone, the combined therapy significantly increases the cure rate and reduces mortality, time to atropinization and duration of hospitalization. Based on the pooled data from this study, it seems likely that combining penehyclidine with atropine leads to the best outcomes for OP poisoning patients. Given the pharmacokinetics of penehyclidine and its ease of use, potentially having the medication be given by pre-hospital staff in cases of likely OP poisoning is in intriguing avenue of further study.[40]

This study has some limitations. First, all the included RCTs were carried out in China. Although not surprising considering that Chinese patients make up a majority of OP poisoning cases worldwide, it would have been better to have more geographical diversity represented. Second, the methodological quality of the included studies was also relatively low, especially concerning the procedures for allocation concealment and blindness. Third, baseline characteristics such as the amount of OP ingested, baseline serum AchE levels, and dose of atropine and penehyclidine administrated were not reported in most studies. In particular, the dosing of atropine is known to very considerably due to a lack of standardization in treating OP poisoning patients. Fourth, some important outcomes such as the rate of ICU admission and intubation rates were lacking. Finally, it is possible that a more careful administration of atropine could lead to a significant improvement in mortality.[41,42] We are unsure as to why the time to atropinization was significantly reduced in the penehyclidine groups and further study is urgently needed. Additionally, the economic effects of adding penehyclidine (such as its effect on overall medication costs) are still unknown.

Despite of these limitations, our meta-analysis synthesized the most up to date RCTs comparing the outcomes of penehyclidine added to atropine for OP poisoning patients. Our study suggests that combining penehyclidine with atropine for OP poisoning patients until atropinization improves overall outcomes for OP poisoning patients by increasing the cure rate, reducing mortality, time to atropinization, time to AchE recovery, IMS rate and total ADR. Nevertheless, current results are based on studies of relatively poor methodological quality and small sample sizes. Despite the favorable outcomes these studies reported, a single-center RCT cannot provide enough additional evidence for the use of penehyclidine in OP poisoning patients. We believe that our updated meta-analysis provides the current best evidence for the use of penehyclidine in conjunction with atropine on OP poisoning patients, and a future multicenter, large scale RCT is still needed to best determine the effectiveness, economics and proper dosing protocol of penehyclidine combined with atropine therapy for OP poisoning patients.

CONCLUSION

Penehyclidine combined with atropine for OP poisoning patients is likely to improve mortality and overall clinical condition. Future high-quality multicenter RCTs are still needed to determine best administration procedures for these drugs.

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