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Review Article

Efficacy of haemoperfusion therapy in patients with paraquat poisoning: a meta-analysis

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Abstract: Paraquat (PQ) poisoning is a public health concern because there is no specific antidote. The effect of haemoperfusion (HP) in clearance of plasma PQ is conflict. The aim of this study is to determine the efficacy and safety of HP therapy in paraquat-poised patients. Bibliographic literature searches were conducted in PubMed, Web of Science and CNKI databases. Pooled data were analyzed by calculating relative risk ratios (RRs) with 95% confidence intervals (CIs), and mean differences (MDs) with 95% CIs for continuous outcomes. The outcomes included mortality, incidence of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS), the levels of alanine transaminase (ALT), partial pressure of oxygen (PaO_2), aspartate aminotransferase (AST), creatinekinase (CK), creatinekinase-MB (CK-MB) and Cr (creatinine). Forty-three studies met the inclusion criteria, including 1291 patients in the experimental group and 1026 patients in the control group. HP therapy significantly reduced the mortality of patients with PQ poisoning (RR = 0.60; 95% CI = 0.54-0.66) compared with conservative treatment. Furthermore, HP therapy significantly decreased the occurrence of ARDS and MODS; and lowered the levels of AST, CK, CK-MB and Cr, while there was no statistical difference in ALT and PaO_2. Besides, comparing with traditional HP, we found that intensive HP therapy reduced the mortality of patients with PQ poisoning (RR = 0.79; 95% CI = 0.68-0.91). In conclusion, HP therapy significantly reduced the mortality of patients with PQ poisoning, and intensive HP therapy had a better effect than traditional HP.

Keywords: Paraquat poisoning, haemoperfusion, meta-analysis

Introduction

Paraquat (PQ, 1, 19-dimethyl-4, 49-bipyridinium chloride) is a non-selective herbicide, which has been widely used as an herbicide since 1955 [1]. PQ is a highly toxic compound without a specific antidote. In humans, thousands of individuals die from PQ intoxication every year by ingesting the pesticide accidentally or intentionally, the mortality rate of PQ intoxication is between 60% and 80% [2]. As we all know, PQ can cause serious damage to organs, including the liver, myocardium, kidneys, and especially the lungs [3]. The prognosis of patients with multiple organ dysfunction syndrome (MODS) and acute respiratory distress syndrome (ARDS) is extremely dangerous. Since the first case report of PQ poisoning, studies have focused on effects of different combination therapies with various agents [4, 5]. PQ poisoning is a major cause of mortality for thousands of people in less-developed countries.

As there is no specific antidote for PQ, the main treatment at present is comprehensive medical management. Poison removal through digestive and circulatory system is the most frequently used therapy strategy [6]. The extracorporeal elimination including haemoperfusion (HP), hemodialysis (HD), hemofiltration (HF), plasma exchange, sequential blood purification, and continuous veno-venous hemofiltration (CVVH), of which HP is more efficient in the clearance of plasma PQ [7]. HP was first used in the 1960's for barbiturate, initially with uncoated columns, subsequently with coated charcoal. After these initial reports, HP has been attempted in the treatment of other poisoning, including paraquate [8]. Recently, many studies focused on the relationship between HP and

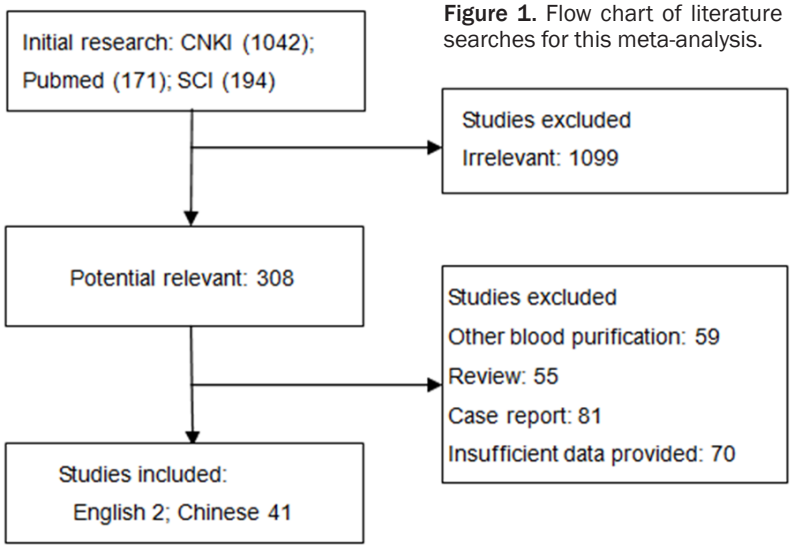

Figure 1. Flow chart of literature searches for this meta-analysis.

the overall prognosis of PQ poisoning. Unfortunately, the results were discouraging and controversial [9, 10].

We screened two English and one Chinese databases in order to collect more articles. Finally, 43 studies were included to perform this systematic review and meta-analysis. The primary aim of our paper is to clarify the therapeutic effect of HP in the PQ intoxication. Then we compared the therapeutic efficacy between intensive HP and traditional HP. The main outcome was mortality; the secondary outcomes were the incidence of ARDS and MODS and the value of AST, ALT, CK, CK-MB, and PaO_2.

Materials and methods

Data sources

A systematic search was performed in PubMed (www.ncbi.nlm.nih.gov/pubmed), Web of Science (SCI) (http://webofknowledge.com/) and CNKI (http://epub.cnki.net/) to screen relevant studies, till the last search updated on 8th November, 2016. The search terms were (paraquat and hemoperfusion). To identify additional studies, references lists of the selected articles were searched.

Data extraction

The screening process was carried out by two investigators independently under the same criteria (**Figure 1**). Disagreements about eligibility were settled by consensus with a third investigator. The following details were extracted from each study: first author, publication date, country, sample number of cases and controls, mortality, Secondary outcomes, including ARDS, MODS, alanine transaminase (ALT), partial pressure of oxygen (PaO_2), aspartate aminotransferase (AST), creatinekinase (CK), creatinekinase-MB (CK-MB), and creatinine (Cr) (**Table 1**).

Selection criteria

Studies included in the meta-analysis had to meet the following criteria: (i) addressing about PQ and HP; (ii) full-text papers; and (iii) original randomized controlled trial (RCT) studies; Studies were excluded if one of the followings existed: (i) reviews; (ii) incomplete data; (iii) case reports; and (iv) other blood purification.

Quality assessment

We carefully assessed each included paper following Jadad score method to guarantee the quality of our meta-analysis. This method assesses the adequacy of randomization, blinding, and loss to follow-up and exit; low quality studies have a score of ≤ 2 and high quality studies have a score of ≥ 3 [11].

Statistical analysis

The meta-analysis was conducted using RevMan4, a copyrighted freeware developed by the Cochrane Collaboration (http://www.cochrane-net.org/revman). Heterogeneity among different studies was measured by calculating χ^2 and I^2. Substantial heterogeneity was indicated if $P < 0.05$ and $I^2 > 50\%$, when a random effects model should be selected; otherwise, if homogeneity was suggested ($P > 0.05$ and $I^2 < 50\%$), a fixed-effects model was used. The primary outcome was reported as pooled relative risk (RR) with 95% confidence intervals (CI) for dichotomous outcomes, and mean differences (MDs) with 95% CIs for continuous outcomes. To investigate the potential of publication bias, we checked the asymmetry of the funnel plot of the included studies. The main outcome was mortality, the secondary outcomes were select-

Table 1. Characteristics of the 43 included studies in this meta-analysis

References	HP (n/N)		CT (n/N)		Secondary outcomes	Jadad
Tabei K (1982)	10	15	6	8	\	2
Zhou QZ (2003)	8	20	18	20	\	2
Deng ZX (2005)	15	24	15	20	\	2
Shan YH (2006)	5	24	13	18	\	3
Sun JS (2006)	8	30	18	36	\	2
Zhang ZY (2006)	2	24	9	23	\	3
Zhao JW (2006)	3	10	10	13	ARDS, MODS	2
Zhao T (2006)	6	22	11	16	\	3
Fu XD (2009)	15	22	18	20	\	2
Wang BL (2009)	4	14	6	8	ARDS, MODS	2
Wang YP (2009)	15	29	24	27	\	2
Xu SY (2009)	10	30	29	36	\	2
Yang R (2009)	14	22	14	16	ARDS	2
Li JL (2010)	6	94	18	89	\	2
Ru GX (2010)	5	33	14	36	ALT, Cr, PaO_2, CK,	2
Jiang HM (2011)	9	28	13	25	ARDS, MODS, ALT, Cr, AST, CK, CK-MB	3
Yu H (2011)	7	15	14	16	ARDS, MODS, ALT, PaO_2, AST, CK, CK-MB	2
Zhang YA (2011)	7	29	14	28	ARDS	2
Zhou DM (2012)	10	28	17	21	\	2
Lin T (2013)	19	39	24	33	\	3
Zhou XM (2013)	13	35	17	27	ARDS, MODS	2
Gu BH (2014)	15	28	19	23	\	3
Hu PB (2014)	23	52	10	13	\	2
Jia RH (2014)	2	22	8	21	\	3
Liu JL (2014)	19	64	34	64	\	3
Liu YW (2014)	13	25	15	20	\	2
Lu SX (2014)	5	15	9	11	\	2
Lv X (2014)	7	20	7	12	ARDS, MODS	2
Tang YD (2014)	2	22	8	22	\	3
Mo J (2015)	16	25	12	14	ALT, Cr, PaQ_2, AST	2
Li A (2016)	37	65	59	75	\	2
Luo FY (2016)	52	117	44	76	\	2
Pang SY (2016)	0	30	7	33	\	2
Wang HX (2016)	38	54	46	56	ALT, Cr, PaO_2, AST, CM-MB	2
Zhang HM (2016)	5	20	14	20	ARDS, MODS	4
Zhang XJ (2016)	5	30	16	30	ARDS, MODS	4
\	Intensive HP		Traditional HP		\	\
Chen LM (2012)	10	28	17	24	\	2
Cheng L (2013)	6	12	9	15	\	2
Huang Y (2013)	22	57	24	51	\	2
Yan XX (2014)	12	33	9	26	\	2
Liu YY (2015)	10	16	18	25	\	4
Mo J (2015)	14	26	16	25	\	2
Le YJ (2016)	4	13	10	13	\	2
Wang HX (2016)	66	115	38	54	\	2
Yan CY (2016)	17	32	19	31	\	2

n: numbers of death patients; N: numbers of total patients; HP: hemoperfusion; CT: conservative treatment; ARDS: acute respiratory distress syndrome; MODS: Multiple Organ Dysfunction Syndrome; ALT: alanine transaminase; PaO_2: partial pressure of oxygen; AST: aspartate aminotransferase; CK: Creatinekinase; CK-MB: Creatinekinase-MB.

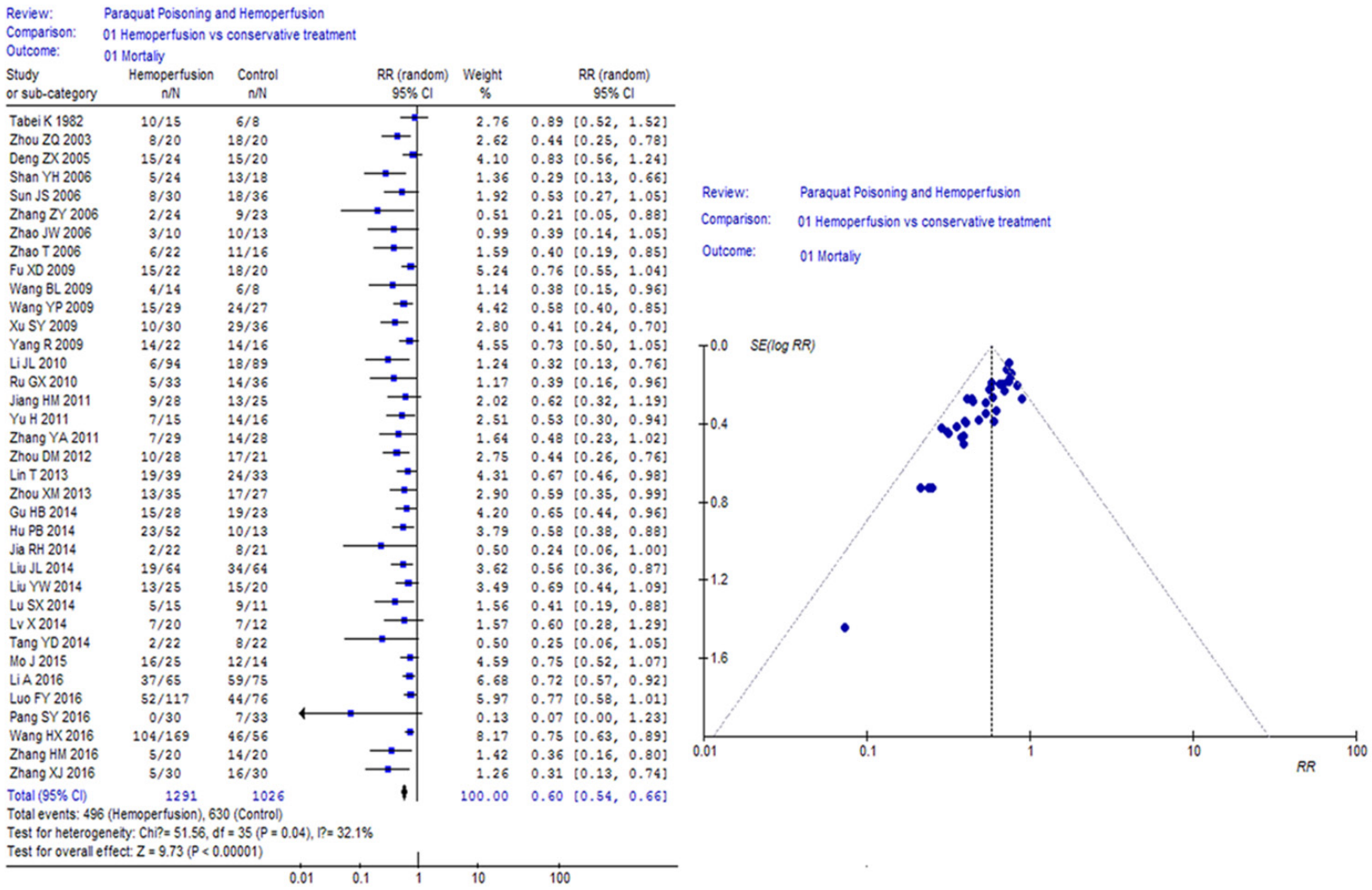

Figure 2. Forest plot showing effect of haemoperfusion therapy on mortality of patients with PQ poisoning.

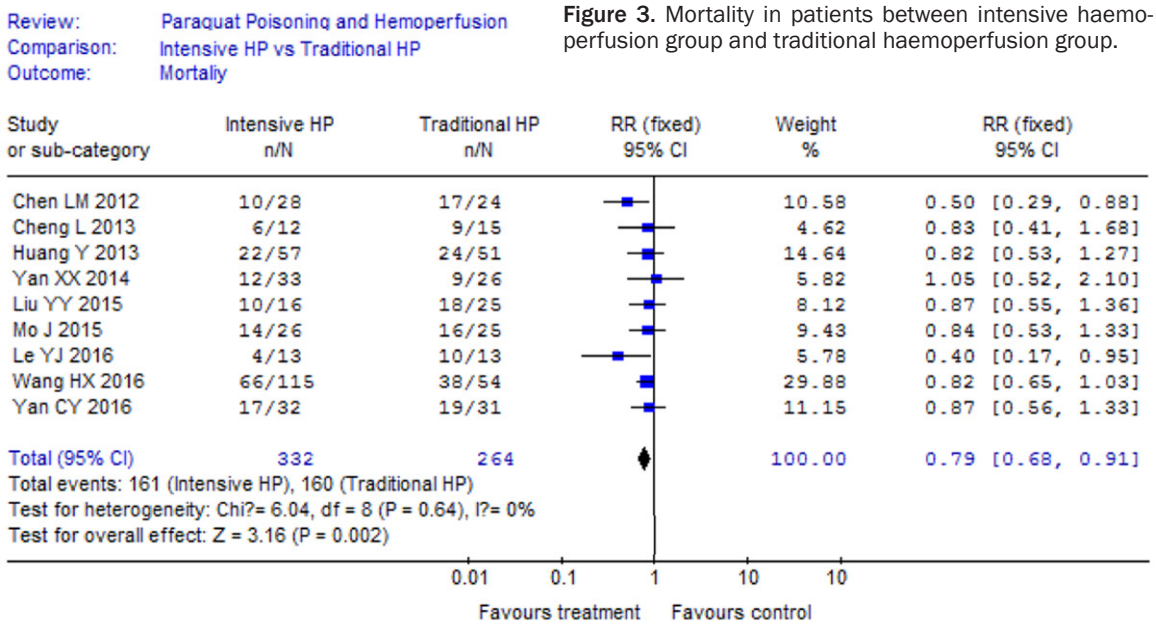

Figure 3. Mortality in patients between intensive haemoperfusion group and traditional haemoperfusion group.

ed according to the numbers of reported articles, which was reported by three or more studies was selected.

Results

Study selection

The process of search strategy is shown in **Figure 1**. Our initial search found 1407 articles. After scanning titles and abstracts, 1099 citations were excluded, and 308 were retained for further reading, 265 articles were excluded after retrieving. In the end, 43 articles complied with the criteria.

Characteristics and quality of the studies included

The main characteristics of the 43 selected studies are presented in **Table 1**. Thirty-six articles reported the effect of hemoperfusion (HP) versus conservative treatment in PQ intoxication [12-47]; 9 reported the effect of intensive hemoperfusion versus traditional hemoperfusion [41, 45, 48-54]. Forty-one of 43 selected studies are in Chinese, and two are in English [12, 42].

On the basis of the criteria described previously [11], 12 of 43 articles mentioned random, only two studies described the special method of randomization. All RCTs described the main outcome at final follow-up. However, double blinding was impossible in all RCTs. Twelve studies were evaluated as high quality, with scores of three or more; and 31 studies were of low quality, with 2 stars or fewer (**Table 1**).

The main outcome: mortality

Thirty-six articles reported the effect of hemoperfusion versus conservative treatment in PQ intoxication, covering 2317 patients. 38.4% (496/1291) patients died in the hemoperfusion therapy group while 61.4% (630/1026) patients died in the conservative treatment group. The χ^2 and I^2 were 51.56 (P = 0.04) and 32.1%, respectively, suggesting heterogeneity. The random-effects model was applied to analyze the data. The pooled RR was 0.60 (95% CI = 0.54-0.66), and the overall effect Z value was 9.73 (P < 0.0001), which suggested that the use of HP therapy significantly reduced the mortality of patients with PQ poisoning. The visual examination of the symmetry of the funnel plot did not suggest a significant publication bias (**Figure 2**).

Furthermore, we conducted a meta-analysis of intensive HP and traditional HP of 9 articles, covering 596 patients (**Figure 3**). The intensive HP mainly focused on increasing the times of HP therapy. 48.5% (161/332) of patients died in the intensive HP group while 60.6% (160/264) of patients died in the traditional HP group, the aggregated results of these studies suggest that the use of intensive HP therapy

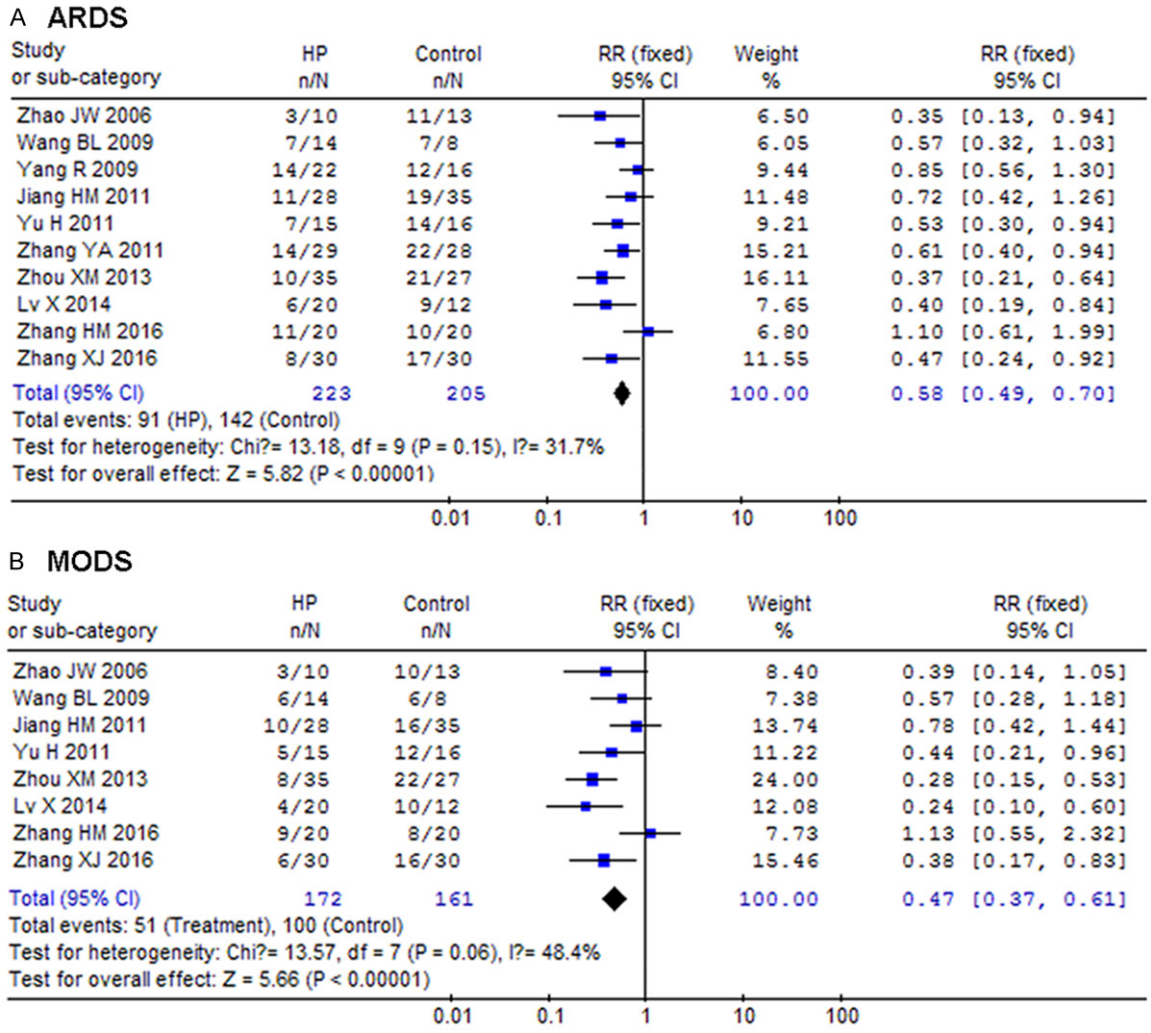

Figure 4. Incidence of ARDS and MODS in patients between haemoperfusion group and conservative treatment group.

reduced the mortality of patients with PQ poisoning (RR = 0.79; 95% CI = 0.68-0.91, P < 0.002). There was no heterogeneity, thus we used a fixed-effects model.

The secondary outcomes

Ten studies reported the incidence of ARDS after the therapy of HP, covering 428 subjects (**Table 1**; **Figure 4A**). There was no heterogeneity, so we selected the fixed-effects model. Compared with the conservative treatment, the HP therapy group significantly decreased the occurrence of ARDS (40.8% vs. 69.3%; RR = 0.58; 95% CI = 0.49-0.70, P < 0.000001). Ten studies reported the incidence of MODS after the therapy of HP, including 333 patients (**Table 1**; **Figure 4B**). No heterogeneity was found, so we used the fixed-effects model. Compared with the conservative treatment, the HP therapy group significantly decreased the occurrence of MODS (29.7% vs. 62.1%; RR = 0.47; 95% CI = 0.37-0.61, P < 0.00001).

Five studies including 302 patients reported the change of ALT in the HP group and conservative treatment group (**Figure 5A**). There was heterogeneity among the included articles, so we used the random-effects model. Two treatment groups had no significant difference in reducing ALT (RR = 0.53; 95% CI = -1.96-3.02, P = 0.68). Four studies involving 233 patients reported the change of AST between the two groups, (**Figure 5B**). Two treatment groups had significant difference in reducing AST (RR = -1.66; 95% CI = -3.08 - -0.25, P = 0.02). There

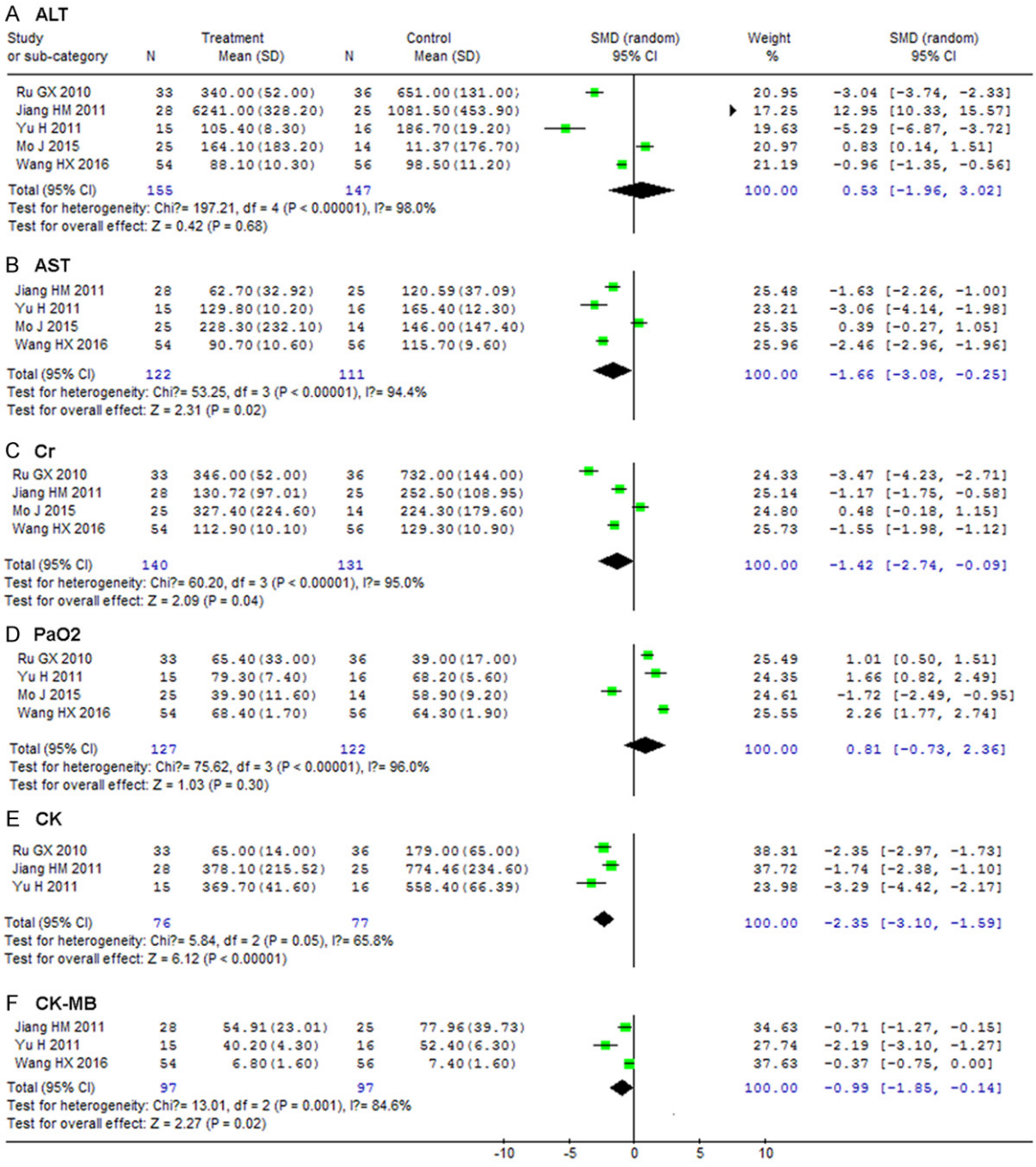

Figure 5. Levels of AST, CK, CK-MB, Cr, ALT and PaO_2 in PQ poisoning patients after treatment of haemoperfusion and conservative therapy.

was heterogeneity among the included articles, so we used the random-effects model.

Four studies covering 271 patients reported the change of Cr between the groups with and without HP (**Figure 5C**). There was heterogeneity among the included articles, so we used random-effects. Two treatment groups had statistical difference in reducing Cr (RR: -1.42; 95% CI = -2.74 - -0.09, P = 0.04). Four studies reported the change of PaO_2, including 249 patients (**Figure 5D**). There was heterogeneity among the included articles, so we used the random-effects model. Statistical difference was not found between the two treatment groups in increasing PaO_2 (RR = 0.81; 95% CI = -0.73-2.36, P = 0.30).

Three studies including 153 subjects reported the change of CK between the groups with and

without HP (**Figure 5E**). There was heterogeneity among the included articles, so we used the random-effects model. Two treatment groups had significant difference in reducing CK when using random-effects model (RR = -2.35; 95% CI = -3.10 - -1.59, P < 0.00001). Three studies reported the change of CK-MB, involved 194 patients (**Figure 5F**). Two treatment groups had statistical difference in reducing CK by using random-effects model (RR = -0.99; 95% CI = -1.85 - -0.14, P = 0.02).

Discussion

PQ is one of the most widely used herbicides in the world. In developing countries, it is often used to suicide due to its widespread availability, low toxic dose, and relatively low cost. Thousands of people die from PQ intoxication every year. HP is an effective therapy that has been used clinically [10]. Many studies have been focused on the correlation between HP and the mortality of PQ poisoning; however, the results of these studies were conflicting [9]. As far as we know, this is the first meta-analysis about the therapeutic effects of HP treatment and conservative treatment in English, which is of profound significance to promote the communication of PQ poisoning therapy strategies among different countries. In this meta-analysis, we included 43 articles to calculate the effect of HP on PQ intoxication. We found that HP therapy significantly reduced the mortality of patients with PQ poisoning (38.4% *vs.* 61.4%; RR: 0.60; 95% CI: 0.54, 0.66). The results of this study were in accordant with two meta-analysis in Chinese [55, 56].

A further comparison between intensive HP and traditional HP indicated that intensive HP therapy markedly lowered the fatality of patients with PQ poisoning (48.5% *vs.* 60.6%; RR: 0.79; 95% CI: 0.68, 0.91). The intensive HP was mainly increased the times of HP therapy. Besides, the therapeutic effects of HP in paraquat-poisoned patients can be influenced by plasma PQ concentration and the length of time before initiating therapy [57, 58]. More clinical studies should pay attention on these problems.

In the early stage of PQ poisoning, the main clinical manifestation is gastrointestinal erosion and ulcer. The level of drug concentration in the lung is highest. The primary cause of mortality in PQ poisoning is often due to acute alveolitis and pulmonary fibrosis. The prognosis of patients with PQ poisoning depends on the incidence of ARDS and MODS [59]. In this study, the HP therapy group significantly decreased the occurrence of ARDS (RR: 0.58; 95% CI: 0.49, 0.70) and MODS (29.7% *vs.* 62.1%; RR: 0.47; 95% CI: 0.37, 0.61) compared with the conservative treatment.

Except the occurrence of ARDS and MODS, the dramatically increasing of AST, ALT, CK, CK-MB, TBIL, LDH and inflammatory factors can cause further damage [1]. Therefore, removing these factors away is essential. We conducted a meta-analysis of these factors, which was reported by three or more articles. The results indicated that HP can significantly reduce the levels of AST, CK, CK-MB and Cr, while there was no statistical difference in ALT between HP group and conservative treatment group. PaO_2 is closely related with lesion of pulmonary [60], however, we found that HP had no significantly effect on PaO_2.

The major limitation of the current meta-analysis is the quality of included studies. Considering of ethical guidelines, PQ poisoning cannot conduct rigorous RCT research, the grouped of experiments and controls were determined by patients themselves or their families. Therefore, the selection bias is unavoidable. Secondly, due to the limited resources, we can only get articles in English and Chinese. In this meta-analysis, in addition to a Japanese literature, others are all Chinese. Thirdly, lacking of standardized treatment, diagnostic and laboratory detection regimen may result in the heterogeneity and impact the results. Clinical studies of the efficacy and safety of PQ poisoning must comply with ethical guidelines. Therefore, it is extremely difficult to design a large-scale randomized control trial to compare the effects of HP therapy with control groups.

In conclusion, this systematic review and meta-analysis showed that HP therapy significantly reduced the mortality of patients with PQ poisoning, and decreased the incidence of ARDS and MODS. Furthermore, HP reduced the levels of AST, CK, CK-MB and Cr, while had no effects on ALT and PaO_2. More well-designed clinical trials are needed to further assess the efficacy and safety of HP therapy in patients with PQ poisoning.

Disclosure of conflict of interest

None.

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