

Does hemoperfusion in combination with other treatments reduce the mortality of patients with paraquat poisoning more than hemoperfusion alone: A systematic review with meta-analysis

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Background: Paraquat (PQ) poisoning is a serious public health problem in many countries. In spite of different treatments, the mortality is still high. We performed a meta-analysis to see whether hemoperfusion (HP) in combination with other treatments reduces the mortality more than HP alone in patients with PQ poisoning. **Materials and Methods:** We searched EMBASE, PubMed, Google Scholar, ISI Web of Knowledge, Cochrane Central Register of Controlled Trials, Scopus, Springer, TRIP, ProQuest, and references of the included studies from January 2000 to August 2017. Two reviewers independently searched and extracted data. We measured I^2 to determine variance contributed by heterogeneity. To investigate the publication bias, Begg's and Egger's tests were used along with funnel plot analysis. **Results:** Ultimately 12 articles were included in the meta-analysis. Five articles compared HP with conventional therapy with a total of 1311 patients, and seven articles compared mortality of patients received HP versus those received HP in combination with an additional treatment. HP alone reduced the odds of death (odds ratio [OR] = 0.20; 95% confidence interval [CI]: 0.11–0.40, $P < 0.0001$) compared to conventional therapy. Furthermore, the odds of death was higher in HP group compared to those received HP in combination of additional treatments (OR = 1.24; 95% CI: 1.05–1.46, $P = 0.01$). **Conclusion:** The mortality was less in HP-treated group compared to those received only conventional therapy. Addition of other treatments with HP reduced the mortality more than HP alone.

Key words: Hemoperfusion, meta-analysis, mortality, paraquat, poisoning

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INTRODUCTION

Paraquat (PQ) poisoning is one of the most serious public health problems.^[1] All body systems, depending on the amount of ingested toxin, are involved in PQ poisoning.^[2] The kidney has been shown to eliminate PQ very effectively; however, some degree of renal failure is observed with acute PQ poisoning.^[3] The

toxic compound accumulates in lung tissue where free radicals are formed and produces alveolitis followed by pulmonary fibrosis.^[4] In spite of different modalities, the mortality is still high in PQ poisoning.^[3-5]

There is no gold standard therapy for PQ poisoning. Activated charcoal or fuller earth, radiation therapy, deferoxamine, cyclophosphamide (CP), methylprednisolone (MP), Vitamin E, Vitamin C,

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hemoperfusion (HP), hemodialysis (HD), continuous venovenous hemofiltration (CVVH), and N-acetyl cysteine (NAC) have been used with varying degrees of success.^[6-14]

Until now, there are five meta-analyses about treatment of PQ poisoning.^[15-19] Agarwal *et al.*, Li *et al.*, and He *et al.* reported meta-analysis about the effect of pulse immunosuppressive and glucocorticoid therapy, which showed a beneficial effect.^[15,16,18] CVVH prolonged the survival time of the patients without significant effect on mortality.^[19] Li *et al.* reported a meta-analysis about the reducing effect of HP on mortality.^[17] However, many studies did not show the beneficial effects.^[20-34] Although the efficacy of pulse immunosuppressive glucocorticoid therapy, CVVH, and HP alone has been shown in above-mentioned meta-analyses, the mortality is still high in single treatment. Since PQ poisoning is a serious public health problem in many countries, we performed a meta-analyses study to see whether HP in combination with other treatments reduces the mortality of PQ poisoning more than HP alone as no reported study yet.

MATERIALS AND METHODS

The project was approved by the Institutional Ethics Committee of our university.

Search strategy

We searched Google Scholar, EMBASE, Pub Med, ISI Web of Knowledge, Cochrane, Scopus, Springer, TRIP, and ProQuest from January 2000 to August 2017. The search strategies included (paraquat) AND (poisoning OR intoxication OR toxicity OR overdose) AND (hemoperfusion OR charcoal hemoperfusion) AND (survival OR death OR mortality OR fatality) in title and abstract based on MESH/subject. The list of references for the studies identified was also examined for more relevant studies.

Data extraction and quality assessment

Inclusion criteria were studies: (1) published articles from January 2000 to August 2017, (2) research was performed on patients (both adults and children) with PQ poisoning, (3) all patients or some of them underwent charcoal HP, (4) outcomes of treatment as death or survival had been reported, and (5) the full text of the published papers was available in English.

Exclusion criteria of this study were as follows: (1) case reports and review articles and (2) studies that all patients received the same treatment. With the use of approved keywords in Mesh, the titles of articles were searched. Then, abstracts in English were extracted. Screening process was carried out by two investigators independently who were

blinded to the objective of the study. The disagreements between two researchers resolved through the involvement of a third researcher in the discussion meeting by considering the reasons for study inclusion and exclusion criteria. Finally, full texts of articles were selected. In the absence of available full text, the article was requested through an E-mail from the authors, research gate, or by librarians in the Isfahan University of Medical Sciences.

We assessed articles by the Critical Appraisal Skills Program (CASP) score method to guarantee the quality of meta-analysis. In this method, the first two questions are screening questions. If the answers were "yes," it was proceeding with the remaining questions. Then, it includes 11 critical questions for randomized clinical trials (RCTs) and case-control studies^[35,36] and 12 question for cohort studies,^[37] evaluating different parts of articles with the answers of "yes" or "no" or "can't tell."

Information about the publication such as name of the first author, year of publication, country of study, type of study, age, PQ concentration, sodium dithionite test, time from ingestion to admission, time to performing HP, HP duration and times, mortality, and follow-up were recorded in the tables.

All patients in the evaluated studies had received some of the following conventional therapy including gastric lavage, activated charcoal, fuller earth, diuretic, dexamethasone, Vitamin C, Vitamin E, NAC, other antioxidants, sodium bicarbonate, glutathione, hormones, cathartics, HD for a patient with acute renal failure if necessary, and other supportive care. However, with respect to using HP alone or in combination with other treatments, we categorized and analyzed our studies based on following two sets.

Set 1: Hemoperfusion (conventional therapy + hemoperfusion) versus nonhemoperfusion (conventional therapy)

This set considers those articles compared mortality between two groups of patients; patients received HP and those not received HP. Both groups had also received conventional therapy as mentioned in the method section.

Set 2: Hemoperfusion versus (Hemoperfusion + other treatments)

This set includes those articles compared the mortality between two groups of patients. Patients in control group received HP, and patients in study group received HP in combination with other treatments. Both groups had also received conventional therapy as mentioned in methods section.

Data analysis

The results analyzed using the comprehensive meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA). Cochrane

test (Q) of heterogeneity was carried out among the studies. For determining the existence of heterogeneity among studies, the significance level was considered as <0.05. Odds ratios (ORs) or relative risk (RR) with 95% confidence intervals (CIs) using forest plot and with the fixed and random effect approach has been analyzed. Heterogeneity was measured by calculating I^2 . Substantial heterogeneity was indicated if $P < 0.05$ and $I^2 > 50\%$ when a random-effects model should be selected. If homogeneity was suggested ($P > 0.05$ and $I^2 < 50\%$), a fixed-effects model was used. The main outcome was mortality. To investigate the publication bias, Begg's and Egger's tests were used along with funnel plot as a graphical test. 95% CI was estimated and included in forest plot.

RESULTS

An initial search identified 2250 records from databases. Considering exclusion criteria, 154 articles had eligibility for full-text evaluation. One hundred and forty-two full-text articles were further excluded, and ultimately 12 articles were selected for meta-analysis including 8 retrospective, 3 RCT, and 1 case-control studies. A flow diagram that detailed the process is presented in Figure 1. Quality assessment of articles showed that CASP score of all 12 articles was higher than 65 which were acceptable.

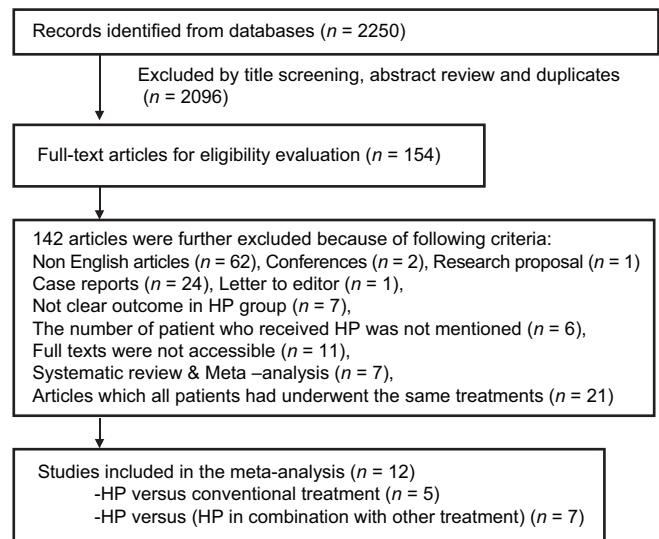
Hemoperfusion (conventional therapy + hemoperfusion) versus nonhemoperfusion (conventional therapy)

The studies included in this set are summarized in Table 1 and Supplementary Table 1. We found 5 articles with a total of 1311 patients.^[38-42] Eight hundred and thirty-seven patients were underwent HP, of which 592 patients died (70.72%). Four hundred and seventy-four patients did not receive HP, of which 428 patients died (90.29%). In a study of Li *et al.*,^[38] because of evaluation of three groups of patients, data of one group were included in this set analysis (HP vs. non-HP) and data of other groups were included in the data set of HP versus (HP + other treatments) which will be explained in the next section.

The mortality rate in one study was the same (100%) in both HP and non-HP groups;^[40] therefore, it did not presented by the software in the funnel and forest plot. The funnel plot showed no publication bias in the studies [Figure 2]. The meta-analysis of this group showed that I^2 was 32.87 ($q = 4.46$, $P = 0.2$) indicating no significant heterogeneity. Using the fixed effect, the OR was 0.20 (95% CI = 0.11–0.40) with $z = 4.604$ ($P < 0.0001$), which showed that the mortality was less in patients received HP compared to those received only conventional treatment [Figure 3].

Hemoperfusion versus (Hemoperfusion + other treatments)

Seven articles included in this set which their results are summarized in Table 2 and supplementary Table 2.^[2,38,43-47]



Abbreviations: HP, hemoperfusion

Figure 1: A flowchart of literature searches in this meta-analysis

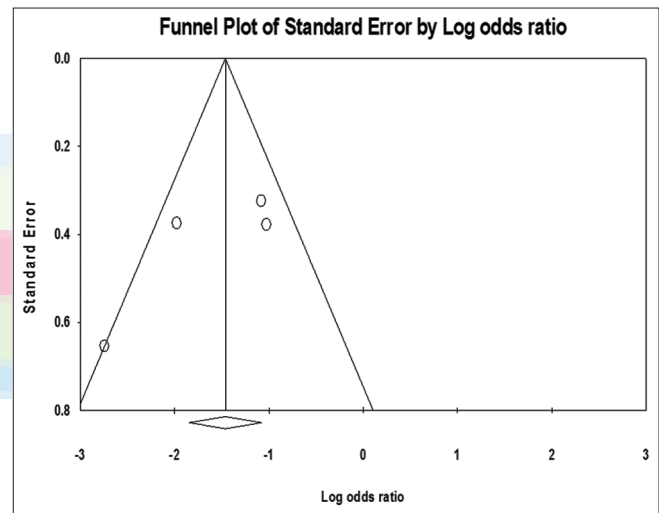


Figure 2: Funnel plot of hemoperfusion and conventional therapy versus conventional therapy in paraquat poisoning mortality

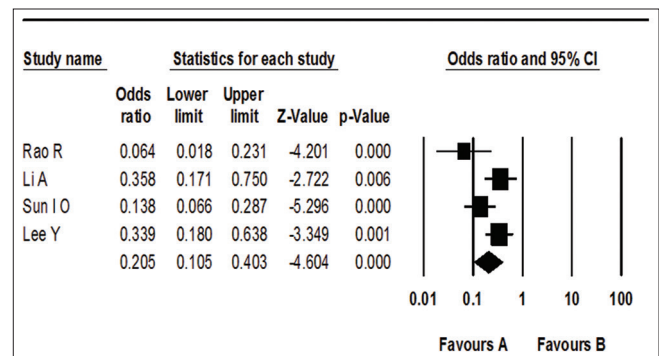


Figure 3: Forest plot for comparison effect of hemoperfusion and conventional therapy (Favor A) versus conventional therapy (nonhemoperfusion) (Favor B) on mortality in paraquat poisoning

Patients in HP group received conventional therapy and HP. Patients in HP in combination with other treatment

group received conventional therapy, HP, and CVVH or continuous renal replacement therapy (CRRT) or CP or/and MP or Chinese medications Xuebijing (XBJ)/Ulinastatin. Analysis of these seven articles evaluated 2881 patients. About 1689 cases were in HP group, and from them, 1174 died (69.50%), and 1192 patients were treated with HP in combination with other treatments, of which 777 died (65.18%).

Begg's tests showed no asymmetry among studies (Kendall's S statistic: 13, $P = 0.07$) indicating no publication bias. The meta-analysis showed that I^2 was 45 ($Q = 11, P = 0.1$) showing no heterogeneity, so using fixed effect model, OR was 1.24 (95% CI = 1.05–1.46 and $z = 2.58; P = 0.01$) which showed that mortality was higher in HP group compared to HP + other treatments [Figure 4].

DISCUSSION

Hemoperfusion versus nonhemoperfusion

Our meta-analysis results showed that mortality was less in patients underwent HP besides conventional therapy compared with those only received conventional treatment (OR: 0.20; 95% CI: 0.10–0.40). Our result is similar to previous meta-analysis.^[17] In Li *et al.* study, HP also reduced mortality significantly (RR: 0.60; 95% CI: 0.54–0.66) and the mortality rate was 38.4% in HP-treated patients which is lower than our analysis. Limited resources of their study which included PubMed, Web of Science

and one Chinese database (China National Knowledge Infrastructure), or publication bias may be the reason.^[17] Although HP reduced mortality, the mortality is still high which seems that other treatments for PQ poisoning should be considered.

Hemoperfusion versus (hemoperfusion + other treatments)

Our results showed patients received HP in combination with other treatments (MP/CP/CVVH/CRRT or XBJ and Ulinastatin) had less mortality compared to those received only HP. With respect to heterogeneity in this result, I^2 was 45 showing no heterogeneity. Two studies showed different results compared with other studies. The mortality of patients received HP was not significantly different from those received HP in combination with CVVH.^[2,44]

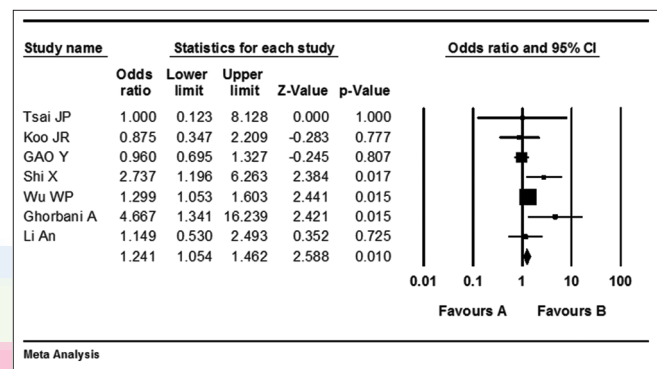


Figure 4: Forest plot of comparison effect of hemoperfusion (Favor A) versus hemoperfusion with other treatments (Favor B) on mortality in paraquat poisoning

Table 1: Information of articles compared patients with paraquat poisoning received hemoperfusion plus conventional therapy (Group 1: Hemoperfusion) versus those received only conventional therapy (Group 2: Nonhemoperfusion)

First author/year	Study design/ area	Sample size (Group 1/Group 2)	Group 1	Group 2	Time to HP (h)	Duration/times of HP	Mortality (%)	F
Rao <i>et al.</i> ^[39] /2017	Retrospective/ India	101 (63/38)	HP + Con. (AC, GL)	Con. (AC, NAC, antioxidants)	33 patients <6 h and 29 patients >6 h	NM/NM	Group 1=42.9 (HP <6 h=6.1 and in HP >6 h=86.20) Group 2=92.10	60 days
Li <i>et al.</i> ^[38] /2016	Retrospective/ China	183 (65/75)	HP + Con. (sodium bicarbonate AC, GL, cathartic, diuresis)	Con. (sodium bicarbonate, AC, GL, cathartic, diuresis)	1-2 h after admission	3-4 h/4 times	Group 1=56.90 Group 2=78.7	60 days
Jagadeesan <i>et al.</i> ^[40] /2017	Retrospective/ India	10 (5/5)	HP + Con. (AC, GL, HD)	Con. (AC, GL, HD)	NM	NM/NM	Group 1=100 Group 2=100	1 h
Sun <i>et al.</i> ^[41] /2016	Retrospective/ Korea	788 (594/194)	HP + Con. (GL, fuller earth, antioxidant, mannitol)	Con. (GL, fuller's earth, antioxidant, mannitol)	NM	NM/NM	Group 1=76.26 Group 2=95.87	3 months
Lee <i>et al.</i> ^[42] /2012	Retrospective/ Korea	272 (110/162)	HP + Con. (GL, fuller's earth, mannitol)	Con. (GL, fuller's earth, mannitol)	NM	NM/NM	Group 1=71.81 Group 2=88.27	3 months

NM=Not mentioned; PQ=Paraquat; HP=Hemoperfusion; AC=Activated charcoal; GL=Gastric lavage; Con=Conventional therapy; NAC=N-acetyl cysteine; HD=Hemodialysis; IH=In hospital; F=Follow-up

Table 2: Information of articles compared patients received conventional therapy plus hemoperfusion (Group 1) versus those received conventional therapy + hemoperfusion + other treatments (Group 2)

First author/ year	Study design/area	Sample size (Group 1/ Group 2)	Group 1	Group 2	Time to HP (h)	HP duration/ times	Mortality (%) Group 1/ Group 2	F
Tsai <i>et al.</i> ^[43] /2009	Case-control/Taiwan	32 (16/16)	HP + Con. (AC)	HP + MP + Con. (AC)	NM	NM	87.5/87.5	7 days
Koo <i>et al.</i> ^[44] /2002	RCT (prospective)/Korea	80 (44/36)	HP + Con. (AC or Fuller's earth, GL, DX, Vit C)	HP + CVVH + Con. (AC or fuller's earth. HP, DX, Vit C)	Group 1: 6.4±3.4 Group 2: 5.7±2.9	6 h/1 or 2 times (Group 1=7.2±3.5 Group 2=5.5±1.7)	63.6/66.7	3 months
Gao <i>et al.</i> ^[2] /2015	Retrospective (RCT)/China	684 (458/226)	HP + Con. (GL, antioxidant, DX, Vit C)	HP + CVVH + Con. (GL, antioxidants, DX, Vit C)	Group 1: 4.8±2.1 Group 2: 5.2±3.7	6 h/1 or 2 times Group 1=5.6±2 Group 2=5.3±2.3	57.4/58.4	IH
Shi <i>et al.</i> ^[45] /2015	Retrospective/china	119 (37/82)	HP + Con. (GL, catharsis, diuresis, hormones, glutathione, and HD for ARF)	HP + XBJ, Ulinastatin + Con. (GL, catharsis, diuresis, hormones, glutathione, HD for ARF)	NM	2-3 h/once daily	70.27/46.34	28 days
Wu <i>et al.</i> ^[46] /2014	Retrospective/Taiwan	1811 (1046/765)	HP + Con.	HP + MP/CP + Con. (DX)	NM	NM/2.0±1.4 S=2.4±1.6 NS=1.8±1.3	75.7/70.7	NM
Ghorbani <i>et al.</i> ^[47] /2015	RCT double blind/IRAN	47 (23/24)	HP + Con. (AC, GL, and HD for renal replacement if necessary)	AC, GL, HP, and HD for renal replacement if necessary, CP, MP	NM	8 h/2 times	60.9/25	IH
Li <i>et al.</i> ^[38] /2016	Retrospective/China	108 (65/43)	HP + Con.	HP + CVVH + Con.	NM	First day: 3-4 h/2 times next 2 day 6-8 h daily	56.90/53.50	60 day

NM=Not mentioned; PQ=Paraquat; HP=Hemoperfusion; Con=Conventional; AC=Activated charcoal; GL=Gastric lavage; CVVH=Continues venovenous hemofiltration; HD=Hemodialysis; S=Survived patients; NS=Nonsurvived patients; DX=Dexamethasone; MP=Methyl prednisolone; CP=Cyclophosphamide; CRRT=Continues renal replacement therapy; IH=In hospital; F=Follow-up; Vit=Vitamin

With respect to mortality, in three studies, CVVH was the additional treatment besides HP, without any significant effect on mortality compared to those received only HP.^[2,38,44] CVVH increased the time to death in the patients. Recent meta-analysis about evaluation of the efficacy of CVVH in the treatment of PQ poisoning supports this issue.^[19]

In three studies, CP/MP was the combination treatments with HP, with good effect on survival.^[43,46,47] In the study of Ghorbani *et al.*, the mortality rate of patients received HP/CP/MP was lower than those underwent HP only (25% vs. 60.9%).^[47] Wu *et al.* reported that patients received HP and MP/CP had lower mortality compared to HP alone (70.7% vs. 75.7%).^[46] However, Tsai *et al.* in a case-control study showed that mortality rate was not significantly different between patients received HP and those received HP and MP.^[43] In the Tsai study, CP was not administered for the patients which may be the reason. Wu *et al.* had investigated different treatment regimen of immunosuppressive therapy, which showed that the MP alone had the least efficacy compared to other compounds.^[46] Of course, the time to performing HP and HP duration has not been mentioned in these two

studies which may be the limitation of their studies.^[43,46] HP duration and early HP may have effects on more removing PQ from the body. The efficacy of MP/CP in reducing mortality has been reported in two previous meta-analyses.^[16,18] The mortality rate had been reported 60.4% and 56.79% in the previous meta-analysis that was performed on the effect of MP and CP on PQ-poisoned patients which is high.^[16,18] It may be due to the fact that patients in the included studies did not receive HP except in one study.^[16,18]

Finally, XBJ/Ulinastatin in combination with HP had protective effects as well. Shi *et al.* reported that patient received HP/XBJ or Ulinastatin had lower mortality compared to HP alone (46.34% vs. 70.27%).^[45] Therapeutic potential of intravenous traditional Chinese has been reported in previous studies.^[48,49]

CONCLUSION

Patients received HP in combination with other treatments (MP/CP/XBJ/Ulinastatin, XBJ) had better prognosis than those received HP alone. When the other

treatments are not available, the HP alone also can reduce mortality compared to conventional therapy. As the mortality is still high, an education on harmful effects of PQ ingestion for the population is necessary to reduce the PQ poisoning.

Limitations of our study are as follows:

1. Data regarding the time from ingestion to admission, amount, and concentration of ingested PQ, blood PQ level, and poisoning severity were not available in all included articles to be able analyze them in the meta-analysis
2. The other potential heterogeneity sources such as time to performing HP and duration of HP therapy (short or long courses) had not been determined in all articles. Due to lack of sufficient data, we could not analyze the outcome with respect to these which can be another limitation of our study.

We may suggest performing future RCT studies considering the severity of poisoning based on blood PQ level to be able determine whether HP alone or HP with other intervention or medications reduces the mortality.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Information of articles compared patients with paraquat poisoning received hemodialysis plus conventional therapy (Group 1: Hemodialysis) versus those received only conventional therapy (Group 2: Nonhemodialysis)

First author/year	Sample size (Group 1/Group 2)	Age (years)	Urine paraquat test	PQ concentration (µg/ml)	Time from ingestion to arrival (h)
Rao <i>et al.</i> ^[39] /2017	101/(63/38)	26.97±7.679	Positive	NM	NM
Li <i>et al.</i> ^[38] /2016	183/(Group 1.1=65/ Group 1.2=43/ Group 2=75)	Median age Group 1=37 Group 2=36	5-200 µg/ml	Group 1=22.95±10.41 Group 2=21.56±11.7	Group 1: 7.5 (0.5-20.5)/ Group 2:12.2 (0.5-22.0) median (range)
Jagadeesan <i>et al.</i> ^[40] /2017	10/(5/5)	Median age, 28.5	NM	NM	2 patients<2 h, 6 patients (2-6 h), 2 patients>6 h
Sun <i>et al.</i> ^[41] /2016	788/(594/194)	S=47±14 NS=59±16	Negative in 26 cases of survival and four cases of nonsurvival group	S=0.4±0.7 NS=80.3±123.1 µg/ml	S=8.7±17.2 NS=6.1±14.4
Lee <i>et al.</i> ^[42] /2012	272 (110/162)	Median age S=49 NS=63	Positive	NM	NM

NM=Not mentioned in the article; S=Survived, NS=Nonsurvived, PQ=Paraquat

Supplementary Table 2: Information of articles compared patients received conventional therapy plus hemoperfusion (Group 1) versus those received conventional therapy + hemoperfusion + other treatments (Group 2)

First author/year	Study design/area	Sample size (Group 1/Group 2)	Age (years)	Urine paraquat test	PQ concentration µg/ml)	Time from ingestion to arrival (hours)	CASP score
Tsai <i>et al.</i> ^[43] /2009	Case-control/ Taiwan	32 (16/16)	Group 1=44.2±15.6 Group 2=43.5±4.2 S=30.25±6.24 NS=45.79±14.56	Positive	Group 2: 47.8±97.3 Group 1: 17.5±20.5 S=0.25±0.19 NS=37.29±74.77	Group 2: 6.4±4.4 Group 1: 6.7±4.8 S=3±1.41 NS=7.04±4.57	82
Koo <i>et al.</i> ^[44] /2002	RCT (prospective)/ Korea	80 (44/36)	Group 1=47±16 Group 2=43±17	2.3% in Group 1 and 2.8% in Group 2 was negative	NM	NM	83
Gao <i>et al.</i> ^[2] /2015	Retrospective/ (RCT) China	684 (458/226)	Group 1=39±15 Group 2=37±19	Group 1=0.1% Group 2=0.2% was Negative	NM	NM	87
Shi <i>et al.</i> ^[45] /2015	Retrospective/ china	119 (Group 1=37/ Group 2.1=43 Group 2.2=39)	Group 1=35.25±8.75 Group 2=33.29±7.66	NM	Group 1=12.26±4.59 Group 2=11.87±6.63	Group 1: 12.31±8.21 Group 2: 10.32±6.47	87
Wu <i>et al.</i> ^[46] /2014	Retrospective/ Taiwan	1811 (1046/765)	S=38.6±14.9 NS=50.4±17.5	NM	NM	NM	
Ghorbani <i>et al.</i> ^[47] /2015	RCT double-blind, IRAN	47 (23/24)	Group 1=23.7±5 Group 2=22.5±5	Navy or dark	NM	Group 1=11 Group 2=15	81
Li <i>et al.</i> ^[38] /2016	Retrospective/ China	183 (65/43)	NM	Urine paraquat concentration 5-200 µg/ml	Group 1: 22.95±10.41 Group 2: 20.82±9.26	Group 1: 7.5 (0.5-20.5) Group 2: 7.8 (0.5-19.0) (median and range)	88

S=Survivals; NS=Nonsurvivals; NM=Not mentioned in the article