



# Systematic review and meta-analysis of the efficacy and safety of immunosuppressive pulse therapy in the treatment of paraquat poisoning\*

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**Abstract:** Paraquat (PQ), a highly effective herbicide, is widely used worldwide. PQ poisoning can cause multiple organ failure, in which the lung is the primary target organ. After PQ poisoning, the patient mortality rate is as high as 90%, and there is currently no specific antidote. The main clinical treatment is the use of glucocorticoids and cyclophosphamide for pulse therapy, but its effectiveness and safety are still uncertain. We investigated the effectiveness and safety of immunosuppressive pulse therapy with glucocorticoids and cyclophosphamide to evaluate the treatment value in patients with acute PQ poisoning. This meta-analysis, combined with seven trials that enrolled a total of 426 patients, showed that immunosuppressive pulse therapy with glucocorticoids and cyclophosphamide for PQ poisoning significantly reduced mortality of the study group (59.3%, 134/226) compared with the control group (81.0%, 162/200). There was no significant difference of hepatitis or renal failure between the control and study groups, indicating that immunosuppressive pulse therapy was relatively safe. Several patients were reported to have leukopenia and returned to normal after 1–2 weeks without any abnormalities. Two cases of non-fatal sepsis were reported and considered to be a side effect of the immunosuppressive pulse therapy. Thus, immunosuppressive pulse therapy can efficiently reduce the mortality of PQ poisoning and it is relatively safe.

**Key words:** Paraquat; Glucocorticoids; Cyclophosphamide; Immunosuppressive pulse therapy; Meta-analysis  
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## 1 Introduction

Emergency departments often encounter many acute diseases, such as trauma (Zhao and Lu, 2014; Zhu et al., 2015) and acute poisoning (Lu et al., 2011;

Jiang et al., 2016). Paraquat (PQ) poisoning is a very common pesticide poisoning in an emergency department. PQ is a high-efficiency herbicide, which is also toxic to the human after ingestion or skin exposure. At present, PQ is still used a lot in agriculture, and PQ poisoning often occurs (Hart, 1987). It is mainly taken in orally and can also be absorbed through skin mucosa and the airway. The early symptoms of PQ intoxication are not obvious: some patients may have no symptoms, or only present with localized corrosive damage such as oropharynx, esophageal mucosa, and contaminated skin; some patients may have nausea and vomiting. However, the disease progresses rapidly after PQ poisoning. Most patients die of severe respiratory failure or multiple

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organ failure within hours or days. The mechanism of PQ poisoning has not been completely clarified, with possibilities including oxidative damage, inflammatory reaction, apoptosis, imbalance of extracellular matrix metabolism, coagulation disorder, and autophagy (Seidenfeld et al., 1978; Dinis-Oliveira et al., 2008). Since there is no specific antidote, various treatment methods are being explored, such as vitamin C and vitamin E. Recently, lysine acetylsalicylate was found to relieve lung damage caused by PQ (Huang et al., 2011). However, these treatments still need to have clinical trials. At present, the most common treatments used in clinical are hemopurification and immunosuppressive pulse therapy (Wang et al., 2017). Studies have found that immunosuppressive therapy of glucocorticoid combined with cyclophosphamide in large dose of these two drugs may cause serious damage to liver and kidney functions (Sakemi et al., 1993; Weissel and Hauff, 2000; Marino et al., 2004). Therefore, we decided to conduct a meta-analysis to assess whether it is safe and effective to treat PQ poisoning with immunosuppressive pulse therapy.

## 2 Methods

### 2.1 Search strategy

We conducted a comprehensive search of the articles on the immunosuppressive pulse therapy after PQ poisoning according to the procedures of the Cochrane Collaboration for Systematic Reviews and Meta-analyses guidelines. The pertinent studies were published before the end of June 2018 as found in PubMed, EMBASE, and Cochrane databases. All these studies were published in English. Search subject keywords were as follows: paraquat, glucocorticoids, and cyclophosphamide.

### 2.2 Inclusion and exclusion criteria

The included studies must meet the following criteria: (1) prospective study; (2) the patient must be  $\geq 16$  years old and PQ was taken orally; (3) the intervention of the experimental group was the pulse therapy of glucocorticoids and cyclophosphamide, and the intervention of the control group was placebo or standard care. Reviews, case reports, letters, and studies without full data were excluded.

### 2.3 Data extraction and quality assessment

In order to avoid errors and improve the accuracy of the results, two researchers were responsible for the data extraction process. One investigator was responsible for extracting the details from the articles and another investigator verified the extracted data for accuracy. Then, these two investigators independently assessed the risk of bias for included studies. The quality assessment of randomized controlled trials (RCTs) was appraised using the Cochrane Collaboration's tool for assessing the risk of bias. The Newcastle-Ottawa Scale (NOS) (Stang, 2010) was used to evaluate non-RCTs.

### 2.4 Statistical analysis

All statistical analyses were performed with Review Manager (RevMan) version 5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity of included studies was evaluated with  $I^2$  statistics. If  $I^2 < 50\%$  and  $P > 0.1$ , there was no heterogeneity between the studies, and the fixed effect model was used for statistical analysis. If  $I^2$  ranged from 50% to 75% and  $P < 0.1$ , the random effect model was used for statistical analysis. If  $I^2 > 75\%$  and  $P < 0.1$ , it indicated that there was obvious heterogeneity between studies, combined analysis cannot be performed, and then only descriptive analysis was performed. Because there were only seven studies included in our meta-analysis, we did not do funnel plots.

## 3 Results

### 3.1 Study selection

Our search method retrieved 273 studies. The studies identified through search were selected in depth screening, and 266 did not meet the predetermined selection criteria. Finally, seven studies (Perriens et al., 1992; Lin et al., 1996, 1999, 2006, 2011; Afzali and Gholyaf, 2008; Ghorbani et al., 2015) met the criteria for inclusion in our research (Fig. 1). There are four RCTs and three non-RCTs.

### 3.2 Characteristics and methodological quality of the studies

Characteristics of included studies in the meta-analysis are described in Table 1. The seven trials

Table 1 Characteristics of studies included in meta-analysis

Author (year)	Area	Study design	Illness severity (control/trial)	No. of patients (male/female)	Trial		Outcome measure	Follow up
					Intervention	Control		
Perriens et al. (1992)	Suriname	Non-RCT		47 (33/14)	MP 8 mg intravenous (iv) qid 14 d; CTX 5 mg/kg iv qd 14 d	Gastric lavage; 10 mg mecloramide iv; Bentonite 30 mg and magnesium sulphate 15 mg in 600 mL water q2 h and mecloramide 10 mg qid	Mortality; respiratory failure; hepatitis; multisystem failure	Not reported
Lin et al. (1996)	Taiwan	Non-RCT	Moderate to fulminant (6NB, 11DB/7NB, 9DB)	57 (29/28)	CTX 1 g iv qd 2 d; MP 1 g iv qd 3 d	Not reported	Mortality; hypoxia; renal failure	Not reported
Lin et al. (1999)	Taiwan	RCT	Moderate to fulminant (9NB, 19DB/8NB, 14DB)	121 (56/65)	MP 1 g iv qd 3 d; CTX 15 mg/kg iv qd 2 d; DEX 10 mg iv q8 h 2 weeks	DEX 10 mg iv q8 h	Mortality; hepatitis; renal failure; hypoxia	3 months
Lin et al. (2006)	Taiwan	RCT	Severe (1NB, 6DB/5NB, 11DB)	23 (16/7)	MP 1 g iv qd 3 d; CTX 15 mg/kg iv qd 2 d, followed DEX 20 mg qd until PaO <sub>2</sub> >80 mmHg. Repeat doses of MP 1 g iv qd 3 d and CTX 15 mg/kg iv qd 1 d (if PaO <sub>2</sub> <60 mmHg)	Gastric lavage with normal saline; activated charcoal was given through a nasogastric tube; two doses of 8 h hemoperfusion therapy; DEX 5 mg iv q6 h until PaO <sub>2</sub> ≥80 mmHg	Mortality; hepatitis; renal failure; hypoxia	6 weeks
Alfali and Gholyaf (2008)	Iran	RCT	Moderate to severe (4NB, 7DB/3NB, 6DB)	20 (9/11)	CTX 15 mg/kg qd 2 d; MP 1 g qd 3 d and mesna 15 mg/kg qd for 4 d	Gastric lavage with normal saline; activated charcoal was given through a nasogastric tube	Mortality; hepatitis; hypoxia; renal failure	Not reported
Lin et al. (2011)	Taiwan	Non-RCT	Severe* (2.5 (0.2, 21)/1.9 (0.2, 21))	111 (59/52)	MP 1 g iv qd 3 d; CTX 15 mg/kg iv qd 2 d; DEX 5 mg q6 h until PaO <sub>2</sub> >80 mmHg. Repeat doses of MP 1 g iv qd 3 d and CTX 15 mg/kg iv qd 1 d (if PaO <sub>2</sub> <60 mmHg)	CTX 2 mg/kg oral qd and DEX 5 mg iv q6 h 14 d	Mortality	60 d
Ghorbani et al. (2015)	Iran	RCT	Moderate to severe (≥NB)	47 (24/23)	MP 1 g iv qd 3 d; CTX 15 mg/kg iv qd 2 d	Gastric lavage; two episodes of 8 h charcoal; hemoperfusion; hemodialysis	Mortality; hepatitis; hypoxia; renal failure	3 d

\* PQ (plasma, mg/L) were presented as median (minimum, maximum); RCT: randomized control trial; MP: methylprednisolone; CTX: cyclophosphamide; DEX: dexamethasone; NB: navy blue color in sodium dithionite; DB: dark blue color; qd: four times a day; qd: once a day; q2 h: every two hours; q8 h: every eight hours; q6 h: every six hours. 1 mmHg=0.133 kPa

enrolled 426 patients. The characteristics extracted from the included trials were: first author/publication year, area, patient samples, study design, illness severity, outcome measurement, follow-up, and therapy characteristics in the experimental and control groups. All except one trial exceeded one clinical outcomes during the treatment. Mortality data were available in all trials. Three studies were followed up for more than 30 d, one was only followed up for 3 d, and the other three did not report. The quality assessment of RCTs is shown in Fig. 2. Three RCTs (Lin et al., 1999, 2006; Ghorbani et al., 2015) described the special method of randomization. One RCT (Ghorbani et al., 2015) used double blinding. The scores on the NOS scale for the remaining three non-RCTs were 7 (Perriens et al., 1992), 6 (Lin et al., 2011), and 5 (Lin et al., 1999), respectively.

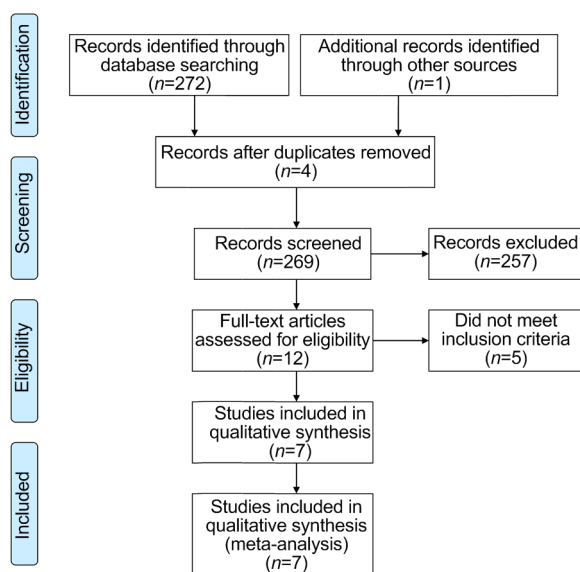


Fig. 1 Literature search strategy

### 3.3 Main outcome: mortality

From the data in Fig. 3, we note that the mortality rate of the study group was 59.3% (134/226), while that of the control group was 81.0% (162/200). These results indicated that pulse therapy with the combination of glucocorticoids and cyclophosphamide efficiently improved survival rate (risk ratio (RR), 0.73; 95% confidence interval (CI), 0.64–0.83;  $P < 0.00001$ ,  $I^2 = 5\%$ ).

### 3.4 Subgroup analysis

In order to analyze factors affecting heterogeneity, we conducted a subgroup analysis based on the illness severity, in which the study was conducted. There were two studies (Lin et al., 1996, 1999) in the fulminant group (one RCT, one non-RCT; RR, 1; 95% CI, 0.94–1.06;  $P = 1.000$ ; Fig. 4) and it showed no heterogeneity. There were seven studies (Perriens et al., 1992; Lin et al., 1996, 1999, 2006, 2011; Afzali and Gholyaf, 2008; Ghorbani et al., 2015) in the moderate to severe groups (four RCTs, three non-RCTs; RR, 0.58; 95% CI, 0.48–0.70;  $P < 0.00001$ ; Fig. 4). The test for heterogeneity was significant ( $I^2 = 57\%$ ).

### 3.5 Sensitivity analysis

To explore the potential source of heterogeneity, we performed a sensitivity analysis. In this meta-analysis, the study by Lin et al. (2011) had the largest sample size, which is an important factor in pooled estimates. In another study conducted by Perriens et al. (1992), the patients did not use hemopurification. Therefore, we performed sensitivity analyses to assess the efficiency of immunosuppressive pulse therapy. We excluded these two studies, which changed RR from 0.58 (0.48–0.70) to 0.37 (0.25–0.55), and there was no heterogeneity in the remaining studies ( $I^2 = 0\%$ ).

### 3.6 Secondary outcomes: renal failure, hepatitis, leucopenia, and hypoxia

All except one drug study (Lin et al., 2011) reported complications separately for the treatment and placebo groups (Perriens et al., 1992; Lin et al., 1996, 1999, 2006; Afzali and Gholyaf, 2008; Ghorbani et al., 2015) (Table 2). Renal failures and hepatitis that occurred within 24 h of admission were considered for non-pharmacological effects and therefore were excluded. Relative risk was calculated for each effect (Figs. 5 and 6). In the remaining studies, there were non-significantly lower rates of renal failure (RR, 0.88; 95% CI, 0.72–1.07; six trials) and hepatitis (RR, 0.92; 95% CI, 0.66–1.27; five trials) when the control group was compared with the study group. Four studies reported that 20 patients suffered from leucopenia, which was significantly higher than the control group (RR, 10.66; 95% CI, 2.18–52.09; four trials). In addition, these patients all spontaneously recovered after 1–2 weeks.

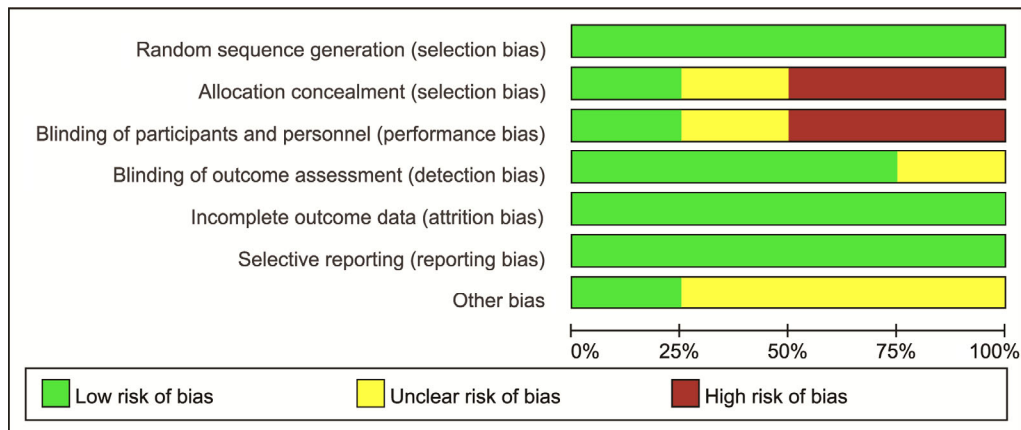


Fig. 2 Quality assessment of the three randomized controlled trials

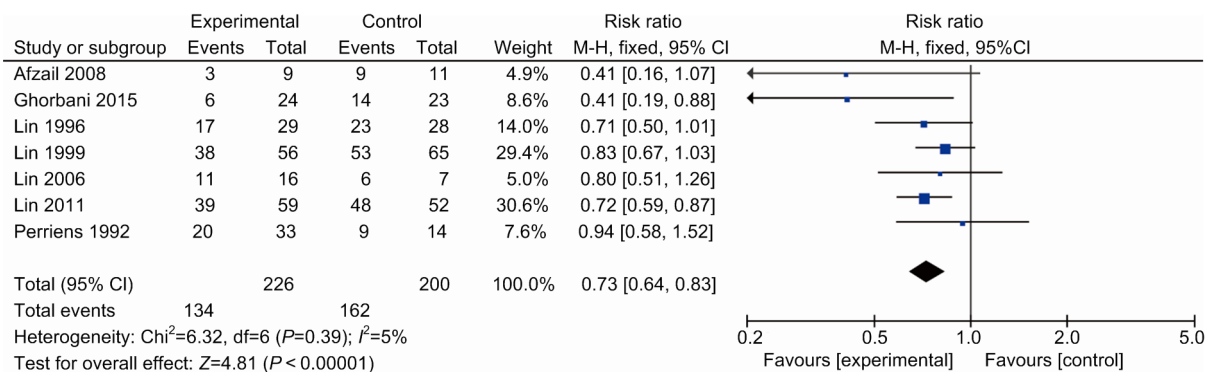


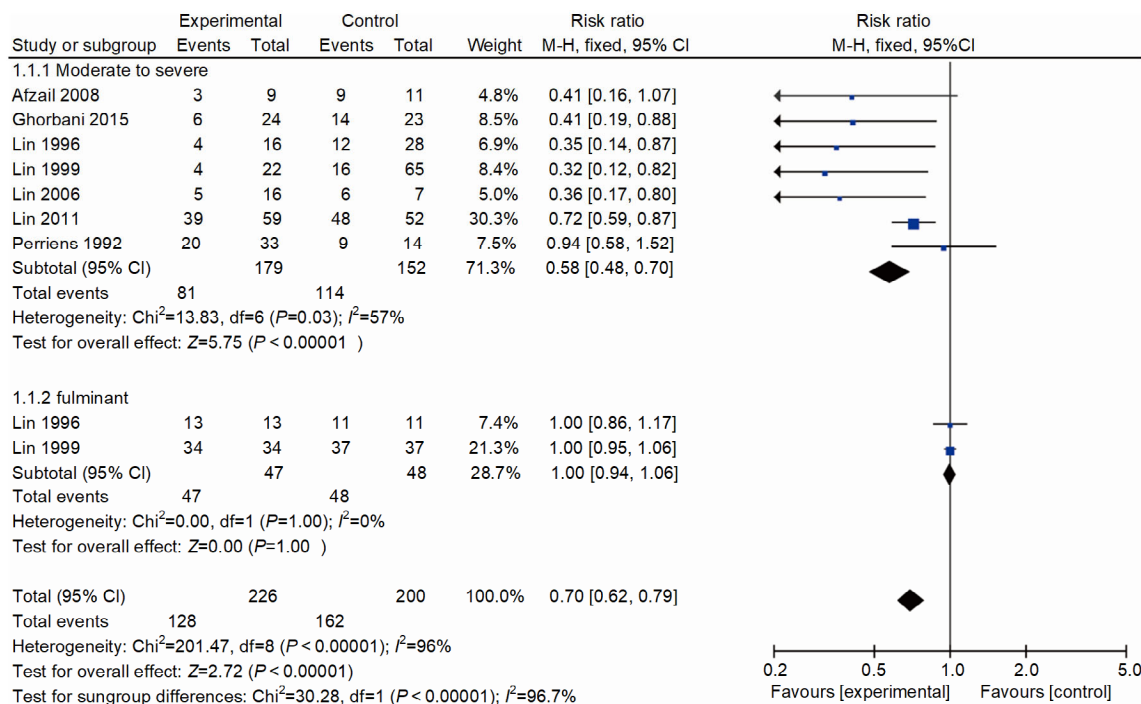
Fig. 3 Forest plot showing effect of pulse immunosuppressive therapy on mortality of patients with PQ poisoning

Hypoxia is the most common symptom in patients with PQ poisoning. Six studies (Perriens et al., 1992; Lin et al., 1996, 1999, 2006; Afzali and Gholyaf, 2008; Ghorbani et al., 2015) reported patients with hypoxia in the experimental and control groups during hospitalization (Fig. 7). We found that the probability of hypoxia in the control group (41.4%) was a little higher than that in the experimental group (36.5%). However, there was no significant difference between the two treatments (RR, 0.74; 95% CI, 0.40–1.35; six trials). It suggested that immunosuppressive pulse therapy may not have an effect on alleviating hypoxia in patients with PQ poisoning.

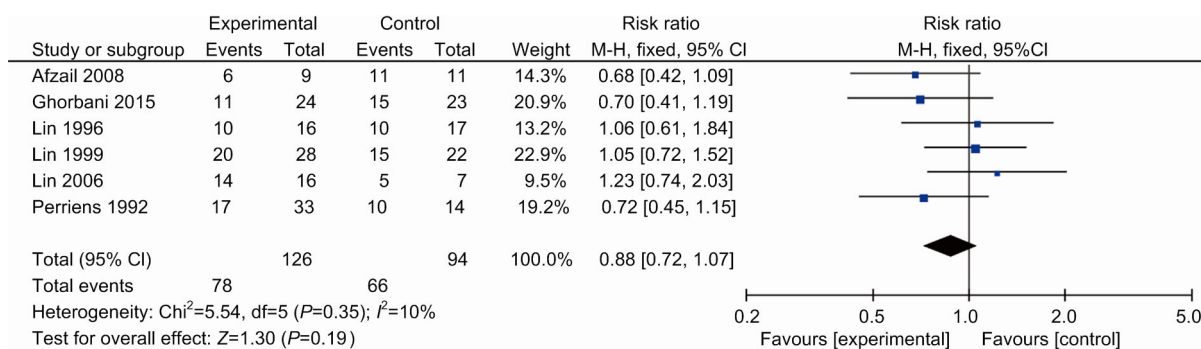
#### 4 Discussion

PQ is widely used because it is highly efficient and environmentally friendly. Its ready accessibility

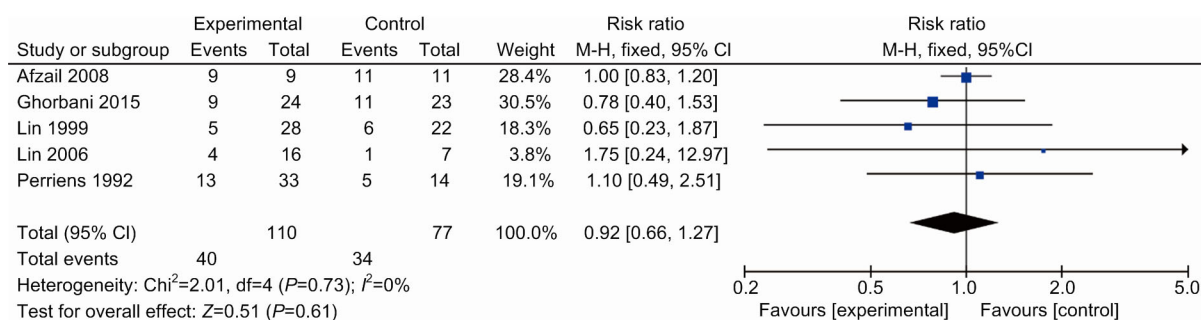
has led to high human exposure due to unintentional contact or intentional suicide. The survival rate after oral poisoning of PQ is related to the amount of intake and the time of poisoning. There is no specific antidote for PQ poisoning at present. Management of the problem is mainly directed at the following aspects: reducing absorption, increasing excretion, anti-inflammatory, anti-oxidation, and supportive treatment. For the first time, in 1988, a study found that the lung damage caused by PQ was probably due to reactive oxygen species (ROS) production. This finding caused a boom in research directed at anti-oxidation treatment (Smith, 1988). Vitamin E and vitamin C were essential trace elements that scavenged oxygen free radicals and proved to play important roles in the process of PQ poisoning. Studies had demonstrated that vitamin E deficiency aggravated lung damage in rats with PQ poisoning (Block, 1979). Vitamin C could release an electron to neutralize



**Fig. 4 Forest plot showing effect of pulse immunosuppressive therapy on mortality in fulminant and moderate to severe PQ poisoning patients**



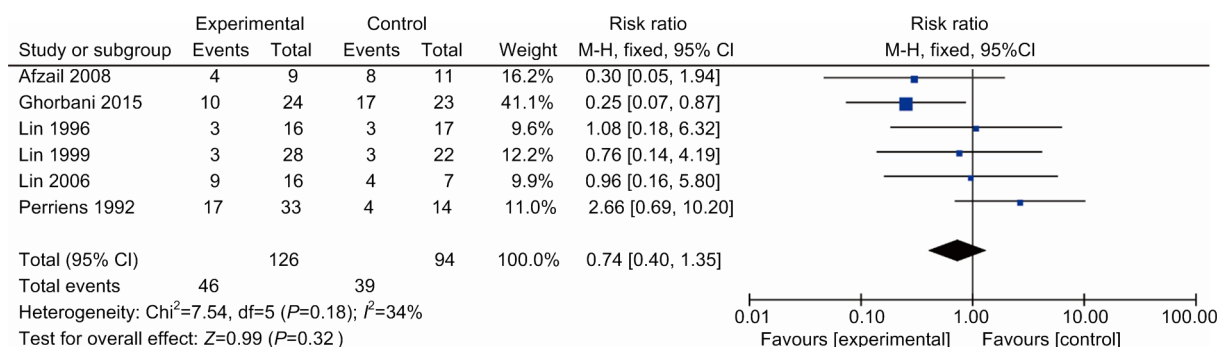
**Fig. 5 Hepatitis in patients between the therapy and control groups**



**Fig. 6 Renal failure in patients between the therapy and control groups**

**Table 2 Outcome data of studies included in meta-analysis**

Author (year)	Study group				Control group			
	Incidence of renal failure	Incidence of hepatitis	Incidence of hypoxia	Incidence of leukopenia	Incidence of renal failure	Incidence of hepatitis	Incidence of hypoxia	Incidence of leukopenia
Perriens et al. (1992)	24/33 (72.7%)	13/33 (39.4%)	17/33 (51.5%)	0/33 (0.0%)	10/14 (71.4%)	5/14 (35.7%)	4/14 (28.6%)	0/14 (0.0%)
Lin et al. (1996)	10/16 (62.5%)		3/16 (18.8%)	6/16 (37.5%)	10/17 (58.8%)		3/17 (17.6%)	0/17 (0.0%)
Lin et al. (1999)	20/28 (71.4%)	5/28 (17.9%)	3/28 (10.7%)	8/28 (28.5%)	15/22 (68.2%)	6/22 (27.3%)	3/22 (13.6%)	0/22 (0.0%)
Lin et al. (2006)	14/16 (87.5%)	4/16 (25.0%)	9/16 (56.3%)	6/16 (37.4%)	5/7 (71.4%)	1/7 (14.5%)	4/7 (57.1%)	0/7 (0.0%)
Afzali and Gholyaf (2008)	6/9 (66.6%)	9/9 (100.0%)	4/9 (44.2%)		11/11 (100.0%)	11/11 (100.0%)	8/11 (72.7%)	
Lin et al. (2011)								
Ghorbani et al. (2015)	11/24 (45.8%)	9/24 (37.5%)	10/24 (41.6%)		15/23 (65.2%)	11/23 (47.8%)	17/23 (73.9%)	

**Fig. 7 Hypoxia in patients between the therapy and control groups**

oxygen free radicals and protected biomolecules before it reacted with other ROS. However, there was no benefit when using vitamin E and C to treat normal rats with PQ poisoning. The reason was not clear. Another attempt to treat PQ poisoning was superoxide dismutase (SOD) enzymes. SOD could catalyze the dismutation of peroxy anion to provide protection. The effect of SOD on the treatment of PQ poisoning is still controversial. A study found that injection of SOD could reduce the mortality of rats with PQ poisoning (Wasserman and Block, 1978), but there was no obvious effect on the human body (Block, 1979). This finding might be related to the physical characteristics of its molecules, which were too large to function through the cell membrane. Therefore, studies had been conducted to embed superoxide in

various media to enable it to enter the cell membrane to function (Day and Crapo, 1996).

The current main treatment for PQ poisoning is inhibition of inflammatory response and pulmonary fibrosis. Inflammatory cells produced large amounts of ROS. Not only that, they also secreted some hydrolase to damage lung cells. Studies showed that inflammatory cells played an important role in the pathological process of PQ poisoning. Immunosuppressive therapy could reduce the inflammatory response of lungs, thereby reducing ROS production and lung damage. Currently, a combination of glucocorticoids and cyclophosphamide is commonly used in the clinical setting.

This meta-analysis showed that pulse therapy with glucocorticoids and cyclophosphamide after PQ

poisoning significantly reduced mortality of the study group compared with the control group.

Except for one study (Perriens et al., 1992), hemopurification treatment was performed on patients with PQ poisoning in both the control and experimental groups. Interestingly, in a recent study on immunosuppressive pulse therapy on PQ poisoning, neither the experimental group nor the control group had hemopurification treatment, and the results showed that there was no statistically significant difference in mortality of these two groups (Gawarammana et al., 2018). It may be that the effect of immunosuppressive pulse therapy alone on PQ poisoning is not effective. Studies had demonstrated that hemopurification in the early stage of PQ poisoning could reduce the mortality of patients (Wang et al., 2017). The immunosuppressive pulse therapy needs to be combined with hemopurification treatment. This combination therapy is also the conventional treatment of PQ poisoning in most hospitals currently. Some scholars believed that PQ could damage the mitochondria by inducing a large amount of ROS, inducing apoptosis, and so on. However, there was no evidence that methylprednisolone or cyclophosphamide could eliminate ROS in the body to protect cell and mitochondria from damage. Therefore, more research is needed to establish the mechanism and role of immunosuppressive therapy on PQ poisoning.

Although previous studies had shown that the high doses of glucocorticoids and cyclophosphamide might cause adverse effects such as hepatitis, renal failure, and leukopenia in patients (Sakemi et al., 1993; Weissel and Hauff, 2000; Marino et al., 2004), our analysis found that there was no significant difference of hepatitis nor renal failure between the control and study groups, indicating that immunosuppressive pulse therapy was relatively safe.

Although several patients were reported to have leukopenia due to the myelosuppressive effect of cyclophosphamide, they returned to normal after 1–2 weeks without any abnormalities. It reminds us to pay attention to the complete blood count (CBC) of the patients during the treatment. Not only that, the patient's immune function was inhibited. In one of the studies (Perriens et al., 1992), two cases of non-fatal sepsis were reported and were considered as a side effect of the immunosuppressive pulse therapy. At

present, immunosuppression is the main drug treatment after PQ poisoning, which could also induce the risk of clinical infection while reducing the inflammatory response. In the process of clinical care, more attention should be paid to protect patients from infection.

After PQ poisoning, patients developed hypoxia due to the inflammation of lungs and pulmonary fibrosis. We found that both the study and control groups in our research had high incidences of hypoxia. However, hypoxia in patients treated with the pulse therapy of glucocorticoids and cyclophosphamide did not achieve remission during hospitalization. Two studies mentioned that the respiratory function of patients who used immunosuppressive therapy recovered slowly 3–6 months after PQ poisoning, nearing normal levels. It suggested that methylprednisolone and cyclophosphamide might have little effect on hypoxia caused by early acute inflammation, but might be able to treat advanced pulmonary fibrosis. However, it may need further research.

Recently, it has been found clinically that some acquired immune deficiency syndrome (AIDS) patients had survived after taking a lethal dose of PQ (Shang and Lu, 2015; Lu, 2018). It was well known that a loss of CD4<sup>+</sup> T lymphocytes was the immune compromise caused by human immunodeficiency virus (HIV). Therefore, we hypothesized that the CD4<sup>+</sup> T lymphocytes cell might play a critical role in the mechanism of body damage caused by PQ (Zhang et al., 2012; Feng et al., 2018). The proposed use of CD4<sup>+</sup> T lymphocytes as a target to guide immunosuppressive therapy to improve the prognosis might be the future direction for the treatment of PQ poisoning.

There were several limitations to our meta-analysis. First, unfortunately not all studies were randomized; some studies had small sample sizes and might increase statistical variance. However, in clinical practice, patients with PQ poisoning were too rare to conduct a large-scale clinical controlled study. Even so, most of the enrolled studies were high-quality clinical trials. Second, there was no uniform standard for the severity of PQ poisoning for patients included in the study, which might increase the heterogeneity between studies and impact on the results. Third, the definition of immunosuppressive pulse therapy was inconsistent. In addition, several known



complications of glucocorticoid and cyclophosphamide such as hyperglycemia, gastrointestinal ulcer, avascular necrosis of the femoral head, or tumor were not discussed in these included studies. Fourth, some studies were not followed up for more than four weeks and could not fully reflect the real effects of immunosuppressive pulse therapy. Despite these limitations, our meta-analysis incorporated all currently available evidence concerning pulse therapy on the treatment of PQ poisoning, and it might have directive sense to clinical work.

## 5 Conclusions

Based on seven studies of immunosuppressive pulse therapy on PQ poisoning, this systematic review and meta-analysis revealed a 21.7% mortality reduction when patients were treated with immunosuppressive pulse therapy (RR, 0.73; 95% CI, 0.64–0.83;  $P < 0.00001$ ,  $I^2 = 5\%$ ). There was no significant difference of hepatitis or renal failure between the control and study groups, indicating that immunosuppressive pulse therapy was relatively safe. Several patients were reported to have leukopenia and returned to normal after 1–2 weeks without any abnormalities. Two cases of non-fatal sepsis were reported and considered as a side effect of the immunosuppressive pulse therapy.

## Contributors

Ying-ge XU and Yuan-qiang LU designed the study, and participated in the data collection and analyses. Ying-ge XU participated in the drafting of the manuscript. Both authors read and approved the final manuscript.

## Compliance with ethics guidelines

Ying-ge XU and Yuan-qiang LU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by either of the authors.

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## 中文概要

**题目:** 关于免疫抑制冲击治疗百草枯中毒的安全性和有效性评价系统回顾和荟萃分析

**目的:** 评估免疫抑制冲击治疗百草枯中毒患者的安全性和有效性。

**创新点:** 报告了在百草枯中毒的患者中, 使用免疫抑制冲击治疗的效果, 确定了其是否会增加患者发生肝炎和肾衰的风险。

**方法:** 我们检索了截止于 2018 年 6 月, 发表在 PubMed, EMBASE 和 Cochrane 三个数据库中关于免疫抑制冲击治疗百草枯中毒患者的文献。经过筛选, 最终有 7 篇文献符合纳入标准, 总共 426 位病人, 并采用 RevMan 软件进行数据分析。

**结论:** 对纳入的 7 篇文献进行荟萃分析, 发现使用免疫抑制冲击治疗能够有效的降低百草枯中毒患者的死亡率, 而且是相对安全的, 不会增加患者发生肝炎或者肾衰的发生率。部分文献报道一些患者出现了白细胞减少, 但都在停药后 1~2 周内恢复正常。另外, 文献还报道了两例非致死性的脓毒症, 这可能是免疫抑制治疗造成的免疫功能低下引起的。

**关键词:** 百草枯; 糖皮质激素; 环磷酰胺; 免疫抑制冲击治疗; 荟萃分析