**Immunosuppressive drugs to reduce the mortality rate in patients with moderate to severe paraquat poisoning: A Meta-analysis**

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**ABSTRACT** — The benefits and adverse effects of immunosuppressive drugs (ISDs) in patients with paraquat (PQ) poisoning have not been thoroughly assessed. This meta-analysis study aims to evaluate the effect of ISDs in patients with moderate to severe PQ poisoning. We searched PubMed, Embase, Cochrane Library, Ovid Medline, CNKI and Wanfang Data from inception to January 2019. The Mantel-Haenszel method with a random-effects model was used to calculate the pooled relative risks (RRs) and 95% Confidence Intervals (CIs) as described by DerSimonian and Laird. An L’Abbé plot was drawn to explore the relationship between the degree of poisoning and mortality. Four randomized controlled trials, two prospective and seven retrospective studies were identified. ISDs were significantly associated with reduced mortality (RR 0.76; 95% CI, 0.58-0.99) and the incidence rate of multiple-organ dysfunction syndrome (MODS) (RR 0.63; 95% CI, 0.48-0.83) in patients with moderate to severe PQ poisoning. They were not associated with an increased incidence rate of hepatitis and reduced incidence rate of acute renal failure and hypoxia. The L’Abbé plot results showed a slight increase in mortality rate in the ISD group with increased mortality in the placebo group. This indicates a possible advantage of ISDs in most of the patients with severe PQ poisoning. These findings suggest that ISDs may reduce the mortality and incidence rate of MODS in moderate to severe PQ poisoning patients, and severe PQ poisoning patients might benefit more from ISDs.

**Key words:** Emergency Medicine, Methylprednisolone, Poisoning, Paraquat

**INTRODUCTION**

Paraquat (PQ) is a highly efficient and non-selective contact herbicide. It has been widely used in many countries since the 1960s because of its strong activity against weeds and rapid deactivation upon contact with the soil. However, it is highly toxic to humans, and there is no specific antidote or effective treatment (Gawarammana and Buckley, 2011; Sun and Lee, 2013). Acute PQ poisoning has occurred more frequently in recent years due to increasing amounts of PQ usage and it has highly fatal side effects (Gawarammana and Buckley, 2011). This has become a major public health problem associated with high mortality rates (> 50%) in developing countries (Chinese College of Emergency Physicians, 2013). To date, there is no specific antidote for acute PQ poisoning, with the mortality rate (50-70%) high in patients that suffer PQ poisoning (Chinese College of Emergency Physicians, 2013; Xu et al., 2017).

Traditional treatment for PQ poisoning includes emetic, gastric lavage, catharsis, diuresis, and other symptomatic treatments (Chinese College of Emergency Physicians, 2013). To some extent, these can clean PQ utility in vivo and vitro, and obviate exposure to PQ. However, these procedures have been proven to be less effective in PQ poisoning.

Apart from its high mortality rate, PQ can also cause severe multiple-organ failure of the pancreas, kid-
neys, liver, lungs, adrenal glands, and central nervous system (Fortenberry et al., 2016; Gawarammana and Buckley, 2011; Li et al., 2015). The mechanism of PQ-induced organ injury is thought to be the production of reactive oxygen species by enzymatic one-electron reduction of PQ, followed by one-electron transfer to dioxygen with the generation of the superoxide anion. Various reactive oxygen species (O2-, H2O2, and OH-) produced from PQ activate the human immune system and induce a variety of inflammatory cytokines (Dinis-Oliveira et al., 2008; Gao et al. Y.X. 2018; He et al. 1992; Hsieh et al. 2013; Jian et al. 2008; Lin et al., 1996, 1999, 2006, 2011; Vieira et al., 1997; Wang et al., 2008; Wu et al., 2014; Xu et al., 2012). However, there are still disagreements between the results of other related studies (Eddleston et al., 2003; Gawarammana et al., 2018; Perriëns et al., 1992), and not enough clinical evidence can prove these results. The study by Perriëns et al. (1992) shows that it is unlikely to improve the prognosis of PQ poisoning and Gawarammana et al. (2018) found no evidence that high dose immunosuppression improves survival in PQ poisoning patients. Hence, we performed this meta-analysis to explore the effect of ISDs in patients with moderate to severe PQ poisoning.

**MATERIALS AND METHODS**

**Literature search**

A systematic search of PubMed, Embase, Cochrane Library, Ovid Medline, CNKI and Wanfang Data, from March 1968 to January 2019 was performed to identify all published studies assessing immunosuppressive therapy for patients with moderate to severe PQ poisoning. The search strategy for PubMed was as follows: (((PQ OR gramoxone)) AND (((((Glucocorticoid OR Methylprednisolone) OR Methylprednisone) OR metacortandracin) OR metacortandralone) OR Cortisone) OR Hydrocortisone) OR Dexamethasone) OR Betamethasone) OR cyclophosphamide). All relevant reports and reviews were hand searched for additional eligible studies. Further information was sought by correspondence with the authors in cases of data unavailability.

**Study selection**

Included studies: (1) Oral PQ poisoning; (2) Patients over the age of 18 with PQ poisoning; (3) Patients in the experimental group received immunosuppressive drugs (Glucocorticoid or Methylprednisolone or Methylprednisone or metacortandracin or metacortandralone or Cortisone or Hydrocortisone or Dexamethasone or Betamethasone or cyclophosphamide); (4) One or more efficacy outcomes were reported, including mortality, incidence rate of MODS, acute renal failure (ARF), hepatitis, and hypoxia.

Excluded studies: (1) Case reports; (2) With no control group; (3) No outcomes were provided relative to the purpose of our studies.

**Data extraction**

Two researchers collected the characteristics of the trials respectively (author, year, study design, sample size, number of ISD group case, number of control group case, population characteristics, use of plasma PQ tests, use of urine PQ tests, application of drugs in the ISD group and control group, and follow-up time), characteristics of the enrolled patients (age, gender, time elapsed to emergency room or hospital, time elapsed from ingestion to the beginning of hemoperfusion), and outcomes (mortality, incubence rate of MODS, ARF, hepatitis, and hypoxia). The primary endpoint was mortality. Secondary endpoints were the incidence of MODS, ARF, hepatitis, and hypoxia. As recommended by the Cochrane Collaboration (Margulis et al., 2014; Panic et al., 2013; Welch et al., 2016; Yoshii et al., 2009), domains of bias of the included studies for efficacy results were reviewed.

**Statistical analysis**

Mantel-Haenszel random-effect meta-analyses were performed for the RCTs, prospective studies, and retrospective studies (Mantel and Haenszel, 1959). Risk ratio (RR) and 95% confidence intervals (CIs) were used as common measures of association between PQ poisoning and outcomes (mortality, incidence of MODS, ARF, hepatitis, and hypoxia) across the studies. An L’Abbé plot was drawn to explore the relationship between the degree of poisoning and mortality (Ho and Tan, 2011). Heterogeneity across the trials was assessed using a standard chi-squared test with a significance being set at P < 0.10. Heterogeneity was also assessed by means of F statistics with significance being set at F > 50%. The random-effects model was used for statistical analyses as described by DerSimonian and Laird (DerSimonian and Laird, 2015). We further conducted subgroup analyses (whether glucocorticoids were used in the ISD group, a dose of cyclophosphamide (CP) <15 mg/kg/day, and period of CP ≤ 2 days) to explore possible explanations for heterogeneity. Statistical analysis was performed using Review Manager (version 5.3).
RESULTS

Characteristics of the studies

The initial search yielded 170 citations, which included 155 studies in English and 15 in Chinese. Four RCTs (Afzali and Gholyaf, 2008; Chen, 2014; Gawarammana et al., 2018; Lin et al., 2006) with 392 patients, two prospective studies (Lin et al., 1999; Perriëns et al., 1992) involving 168 patients and 7 retrospective studies (Jian et al., 2008; Lin et al., 1996, 2011; Vieira et al., 1997; Wang et al., 2008; Wu et al., 2014; Xu et al., 2012) involving 2392 patients met the criteria. Of the 157 excluded articles, 22 were repeated articles, 47 were experiments on animals, 5 were meta-analysis, 41 were not related to the immediate goals of our study, 6 were articles without control groups, and 36 were case reports, (Fig. 1).

The characteristics of the trials included in this study are listed in Table 1. All studies included in the meta-analysis involved patients with moderate to severe PQ poisoning. Of these included studies, a sodium dithionite reaction test was done on the urine samples of all the patients. In most of the studies (Afzali and Gholyaf, 2008; Chen, 2014; Gawarammana et al., 2018; Jian et al., 2008; Lin et al., 1996, 1999, 2006, 2011; Perriëns et al., 1992; Vieira et al., 1997; Wang et al., 2008; Wu et al., 2014; Xu et al., 2012), ordinarily, patients with a navy blue or a dark blue color indicated severe PQ poisoning (Koo et al., 2009; Scherrmann et al., 1987). In most of the studies (Afzali and Gholyaf, 2008; Chen, 2014; Lin et al., 1999, 2006, 2011), immunosuppressive drugs and treatment duration were CP 15 mg/kg/day for 2 days and methylprednisolone (MP) 1g/day for 3 days. Patients in nine of the studies received MP (Afzali and Gholyaf, 2008; Gawarammana et al., 2018; Jian et al., 2008; Lin et al., 1996, 1999, 2006, 2011; Wang et al., 2008; Wu et al., 2014); in six of the studies they were given dexamethasone (DEX) therapy (Gawarammana et al., 2018; Lin et al., 2006, 2011; Perriëns et al., 1992; Vieira et al., 1997; Wang et al., 2008) and Mesna and Cyclosporin A were applied in two of the studies (Afzali and Gholyaf, 2008; Xu et al., 2012). In the control group, one study used MP (Chen, 2014); one study used CP (Lin et al., 2011); and three studies took DEX (Lin et al., 2006, 1999, 2011). The characteristics of patients and the outcomes are shown in Table 2. All the studies reported a patient’s mortality, most studies gave information about age, gender, the time elapsed to the emergency room or hospital, and the time to hemoperfusion. The incidence rate of MODS, ARF, hepatitis, and hypoxia were reported.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>Sample size (experimental/control)</th>
<th>Patients</th>
<th>Plasma PQ tests</th>
<th>urine PQ tests</th>
<th>ISD group</th>
<th>Placebo group</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gawarammana/2017</td>
<td>RCT</td>
<td>Sri Lanka</td>
<td>299 (147/152)</td>
<td>NG</td>
<td>NO</td>
<td>YES</td>
<td>1 g/day</td>
<td>1 g/day</td>
<td>DEX 8 mg/8 hr 14 days</td>
</tr>
<tr>
<td>Chen/2014</td>
<td>RCT</td>
<td>China</td>
<td>50 (25/25)</td>
<td>Moderate to severe poisoning</td>
<td>NG</td>
<td>NG</td>
<td>15 mg/kg/24 hr 2 days</td>
<td>NG</td>
<td>Mesna 15 mg/kg 4 days</td>
</tr>
<tr>
<td>Afzali/2008</td>
<td>RCT</td>
<td>Iran</td>
<td>20 (9/11)</td>
<td>Moderate to severe Poisoning</td>
<td>NO</td>
<td>YES</td>
<td>1 g/24 hr 3 days</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Lin/2006</td>
<td>RCT</td>
<td>Taiwan</td>
<td>23 (16/7)</td>
<td>Severe poisoning</td>
<td>YES</td>
<td>YES</td>
<td>15 mg/kg/24 hr 2 days</td>
<td>NG</td>
<td>DEX 20 mg/24 hr</td>
</tr>
<tr>
<td>Lin/1999</td>
<td>Prospective Study</td>
<td>Taiwan</td>
<td>121 (56/65)</td>
<td>Moderate to severe poisoning</td>
<td>NO</td>
<td>YES</td>
<td>15 mg/kg/24 hr 2 days</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Perriëns/1992</td>
<td>Prospective Study</td>
<td>Suriname</td>
<td>47 (33/14)</td>
<td>NG</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>5 mg/kg/day to a maximum of 4 g 2 weeks</td>
<td>DEX 6 mg/day 2 weeks</td>
</tr>
<tr>
<td>Wu/2014</td>
<td>Retrospective Study</td>
<td>Taiwan</td>
<td>1811 (765/1046)</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>&gt;500 mg</td>
<td>&gt;200 mg</td>
<td>Cyclosporin A 250 mg bid 3 weeks</td>
</tr>
<tr>
<td>Xu/2012</td>
<td>Retrospective Study</td>
<td>China</td>
<td>211 (111/100)</td>
<td>Moderate to severe poisoning</td>
<td>NG</td>
<td>NG</td>
<td>15 mg/kg/24 hr 2 days</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Lin/2011</td>
<td>Retrospective Study</td>
<td>Taiwan</td>
<td>111 (59/52)</td>
<td>Severe poisoning</td>
<td>YES</td>
<td>YES</td>
<td>15 mg/kg/24 hr 2 days</td>
<td>NG</td>
<td>2 mg/kg/24 hr</td>
</tr>
<tr>
<td>Wang/2008</td>
<td>Retrospective Study</td>
<td>China</td>
<td>55 (26/29)</td>
<td>Moderate to severe poisoning</td>
<td>NG</td>
<td>NG</td>
<td>240 mg/8 hr 7 days</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Jian/2008</td>
<td>Retrospective Study</td>
<td>China</td>
<td>136 (69/67)</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>500 mg/day 3 days</td>
<td>600 mg/day 14 days</td>
<td>DEX 8 mg/8 hr 14 days</td>
</tr>
<tr>
<td>Vieria/1997</td>
<td>Retrospective Study</td>
<td>Brazil</td>
<td>35 (25/10)</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>15 mg/kg dl 10 mg/kg dl2, 7 mg/kg dl3-5</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Lin/1996</td>
<td>Retrospective Study</td>
<td>Taiwan</td>
<td>33 (16/17)</td>
<td>Moderate to severe poisoning</td>
<td>NO</td>
<td>YES</td>
<td>1 g/24 hr 3 days</td>
<td>1 g/24 hr 2 days</td>
<td>NG</td>
</tr>
</tbody>
</table>

PQ, paraquat; ISD, immunosuppressive drugs; MP, methylprednisolone; CP, cyclophosphamide; DEX, dexamethasone; RCT, randomized controlled trial; IV, intravenous infusions; NG, not given.
Immunosuppressive drugs in paraquat poisoning patients

in studies 4, 6, 6, 8 respectively.

**Primary Outcome**

All studies were included in the analysis with mortality (Afzali and Gholyaf, 2008; Chen, 2014; Gawarammana et al., 2018; Jian et al., 2008; Lin et al., 1996, 1999, 2006, 2011; Perriëns et al., 1992; Vieira et al., 1997; Wang et al., 2008; Wu et al., 2014; Xu et al., 2012). The pooled result from RCTs and prospective studies showed that immunosuppressive treatment was significantly associated with a reduction of mortality rates (RR 0.76; 95% CI, 0.58-0.99) in patients with PQ poisoning with a moderate to severe PQ poisoning. We found that ISDs were significantly associated with decreased mortality in patients with severe PQ poisoning. The four RCTs and two prospective studies of ISDs and PQ poisoning are presented in an L’Abbé plot. With the increased mortality in the placebo group, the mortality in the ISD group increased slowly, which indicated a possible advantage of ISDs in most of the patients with severe PQ poisoning.

The seven retrospective studies of ISDs and PQ poisoning are presented in an L’Abbé plot. With the increased mortality in the placebo group, the mortality in the ISD group decreased.

**Risk of Bias and Subgroup Analyses**

With the evaluating tools provided by the Cochrane Collaboration (Margulis et al., 2014; Yoshii et al., 2009), risk of bias of four RCTs and two prospective studies were shown in Fig. 6. The selection, attrition and reporting biases were well-controlled in four studies. However, imbalances were reported in the degree of poisoning (Gawarammana et al., 2018; Perriëns et al., 1992), plasma PQ tests (Gawarammana et al., 2018; Perriëns et al., 1992), patients with severe PQ poisoning. The four studies were considered to be of high quality because the random sequence generation, allocation concealment, and blinding were not reported in the articles. Two studies were considered to be of fair quality.

Subgroup analyses for mortality were performed to evaluate whether glucocorticoid MP or DEX was used in the ISD group, and at a dose of CP (CP < 15 mg/kg/day or CP = 15 mg/kg/day) for a period of CP (≤ 2 days) (Table 4). Subgroup analysis results showed no significant differences in the mortality rates in the group that used glucocorticoid (MP or DEX) (RR 0.88; 95% CI, 0.78-0.99), and where the dose of CP was not less than 15 mg/kg/day (RR 0.70; 95% CI, 0.51-0.97) and the period of CP was not more than 2 days (RR 0.70; 95% CI, 0.51-0.97). Results of this subgroup should be explained cautiously due to the finite sample size and potential bias that was inherent to the subgroup analysis.

**DISCUSSION**

Our meta-analysis identified four RCTs, two prospective studies and seven retrospective studies including 2952 patients, to investigate the effect of ISDs on mortality in patients with moderate to severe PQ poisoning. We found that ISDs were significantly associated with decreased mortality and a reduced incidence rate of MODS in PQ poisoning patients, and not associated with an increased incidence rate of ARF, hepatitis, and hypoxia.

In recent years, a large number of clinical tests and
Table 2. Characteristics and outcomes of patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (ISD/Placebo)</th>
<th>Sex (male/female) (ISD/Placebo)</th>
<th>Time elapsed to emergency room or hospital (hr) (ISD/Placebo)</th>
<th>Time to hemoperfusion (hr) (ISD/Placebo)</th>
<th>Mortality (%) n (ISD/Placebo)</th>
<th>ARF (%) n (ISD/Placebo)</th>
<th>Hepatrin (%) n (ISD/Placebo)</th>
<th>Hypoxia (%) n (ISD/Placebo)</th>
<th>MODS (%) n (ISD/Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gawarammana/2017</td>
<td>27 (21-38) / 27 (21-36)</td>
<td>(100/47) / (113/39)</td>
<td>6.6 (4.5-11.9) / 6.0 (4.0-11.0)</td>
<td>NG</td>
<td>(69) 101/ (71) 108</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Chen/2014</td>
<td>NG</td>
<td>NG</td>
<td>(100/47) / (113/39)</td>
<td>NG</td>
<td>(16.0) 4/ (44.0) 11</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Afzali/2008</td>
<td>(27 ± 10) / (25 ± 10)</td>
<td>(8/1) / (8/5)</td>
<td>(5 ± 2) / (4.5 ± 2)</td>
<td>(10 ± 2) / (10 ± 2)</td>
<td>(33.3) 3/ (81.8) 9</td>
<td>(66.7) 6/ (100) 11</td>
<td>(100) 9/ (100) 11</td>
<td>(44.4) 4/ (72.7) 8</td>
<td>NG</td>
</tr>
<tr>
<td>Lin/2006</td>
<td>(33.6 ± 14.3) / (37.0 ± 13.8)</td>
<td>(11/5) / (5/2)</td>
<td>3.0 (0.5-12.5) / 2.0 (10.0, 13.0)</td>
<td>(7.0 ± 4.3) / (7.5 ± 7.3)</td>
<td>(31.3) 5/ (85.7) 6</td>
<td>(87.5) 14/ (71.4) 5</td>
<td>(25.0) 4/ (14.3) 1</td>
<td>(56.3) 9/ (57.1) 4</td>
<td>NG</td>
</tr>
<tr>
<td>Lin/1999</td>
<td>NA</td>
<td>NA</td>
<td>(33/23) / (45/20)</td>
<td>NA</td>
<td>(67.9) 38 / (81.5) 53</td>
<td>(53.6) 30/ (69.2) 45</td>
<td>(44.6) 25/ (44.6) 29</td>
<td>(41.1) 23/ (53.8) 35</td>
<td>NG</td>
</tr>
<tr>
<td>Perriëns/1992</td>
<td>(28.4 ± 12.8) / (28.8 ± 11.9)</td>
<td>(14/19) / (8/6)</td>
<td>NG</td>
<td>(60.6) 20 / (64.3) 9</td>
<td>(73) 24/ (71) 10</td>
<td>(39) 13/ (36) 5</td>
<td>(52) 17/ (29) 4</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Wu/2014</td>
<td>(45.8 ± 17.4) / (48.3 ± 17.8)</td>
<td>(542/223) / (726/520)</td>
<td>NG</td>
<td>(70.7) 545 / (75.7) 792</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Xu/2012</td>
<td>(32.0 ± 15.0) / (34.0 ± 15.0)</td>
<td>(44/15) / (35/17)</td>
<td>(3.5 ± 1.9) / (3.6 ± 1.7)</td>
<td>NG</td>
<td>(44.1) 40 / (64.0) 64</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>(33.3) 37/ (51.0) 51</td>
</tr>
<tr>
<td>Lin/2011</td>
<td>(41.0(18-79) / (32.5(18-79)</td>
<td>(44/15) / (35/17)</td>
<td>3.0 (1.0-21.0) / 3.0 (1.0-21.0)</td>
<td>6.0 (3.5-23.7) / 5.5 (3.0-24.5)</td>
<td>(66.1) 39/ (92.3) 48</td>
<td>NG</td>
<td>(23.7) 14/ (23.1) 12</td>
<td>(28.8) 17/ (23.1) 12</td>
<td>NG</td>
</tr>
<tr>
<td>Wang/2008</td>
<td>(29.5 ± 11) / (29.3 ± 9.9)</td>
<td>(11/15) / (12/17)</td>
<td>(6.1 ± 6.0) / (6.0 ± 5.9)</td>
<td>NG</td>
<td>(42.3) 11 / (72.4) 21</td>
<td>NG</td>
<td>NG</td>
<td>(42.3) 11 / (72.4) 21</td>
<td>(38.5) 10/ (67.0) 20</td>
</tr>
<tr>
<td>Jian/2008</td>
<td>(33.2 ± 17.5) / (30.6 ± 15.8)</td>
<td>(29/40) / (24/43)</td>
<td>NG</td>
<td>(21.7) 15/ (88.1) 59</td>
<td>(1.4) 1/ (8.1) 6</td>
<td>NG</td>
<td>(6.8) 5/ (39.2) 29</td>
<td>(8.1) 6/ (18.9) 14</td>
<td>NG</td>
</tr>
<tr>
<td>Vieria/1997</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>(28.0) 7/ (100) 10</td>
<td>(25.0) 4/ (17.0) 3</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Lin/1996</td>
<td>(29.4 ± 14.4) / (31.7 ± 10.2)</td>
<td>(7.9) / (9.8)</td>
<td>NG</td>
<td>(25.0) 4/ (70.6) 12</td>
<td>(62.5) 10/ (58.8) 10</td>
<td>(37.5) 6/ (29.4) 5</td>
<td>(25.0) 4/ (17.0) 3</td>
<td>NG</td>
<td>NG</td>
</tr>
</tbody>
</table>

ARF, Acute renal failure; MODS, Multiple organ dysfunction syndrome; ISD, immunosuppressive drugs; NG, not given.
case reports indicated that ISDs are beneficial to patients with moderate to severe PQ poisoning. However, several studies showed no improvement with the treatment of ISDs. Of these studies included in our meta-analysis, four RCTs and two prospective studies assessed the effect of ISDs on the mortality of patients with moderate to severe PQ poisoning (Afzali and Gholyaf, 2008; Chen, 2014; Gawarammana et al., 2018; Lin et al., 1999, 2006; Perriëns et al., 1992). Of these six studies, four demonstrated that treatment with ISDs may be beneficial in treating patients with moderate to severe PQ poisoning (Afzali and Gholyaf, 2008; Chen, 2014; Lin et al., 1999, 2006), while two found no significant evidence that ISDs can improve the prognosis of PQ poisoning patients (Gawarammana et al., 2018; Perriëns et al., 1992).

A recent systematic review regarding PQ-induced lung fibrosis treated with ISDs and the need for a better prediction of the outcome showed no possible benefits from immunosuppressive therapy (Eddleston et al., 2003). In this systematic review (Eddleston et al., 2003), four included studies lacked a control group (Addo and Poon-King, 1986; Addo et al., 1984; Botella de Maglia and Belenguer Tarin, 2000; Garcia et al., 2000) and two studies were case reports (Chen et al., 2002; Chomchai, 2003), which may have resulted in low reliability. Our previous studies have shown that ISDs may reduce the incidence of MODS in patients with moderate to severe PQ poisoning (Gao et al., 2018). Another systematic review that assessed the effect of immunosuppressive therapy on PQ-induced lung fibrosis (Li et al., 2014) report-
ed beneficial results with immunosuppressive therapy for patients with PQ-induced lung fibrosis, but in this study, we did not find relevant information about lung fibrosis as this was not reported in three of the included studies (Afzali and Gholyaf, 2008; Lin et al., 1999, 2006). Hence, the results of the study by Li et al. (2014) are not convincing. In the meta-analysis conducted by He et al. (2015) that was completed in 2015, three RCTs (Afzali and Gholyaf, 2008; Lin et al., 1999, 2006) and two retrospective studies (Lin et al., 1996; Vieira et al., 1997) were combined to calculate the pooled relative risks. Because the Cochrane Collaboration did not recommend merging conversion data, the results might be misleading. Though several sensitivity analy-
Table 4. Subgroup analysis of mortality in RCTs.

<table>
<thead>
<tr>
<th>Stratification</th>
<th>No. of Patients (Studies)</th>
<th>No. of Events/No. in Group (%)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of Glucocorticoid (MP or DEX)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>510 (5)</td>
<td>167/261 (64.0)</td>
<td>0.88 (0.78-0.99)</td>
<td>0.06</td>
<td>56</td>
</tr>
<tr>
<td>Non</td>
<td>50 (1)</td>
<td>4/25 (16.0)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doses of CP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 mg/kg/day</td>
<td>47 (1)</td>
<td>20/33 (60.6)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 mg/kg/day</td>
<td>442 (5)</td>
<td>151/253 (59.7)</td>
<td>0.70 (0.51-0.97)</td>
<td>0.01</td>
<td>68</td>
</tr>
<tr>
<td>Period of CP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 Days</td>
<td>442 (5)</td>
<td>151/253 (59.7)</td>
<td>0.70 (0.51-0.97)</td>
<td>0.01</td>
<td>68</td>
</tr>
<tr>
<td>≥2 Days</td>
<td>47 (1)</td>
<td>20/33 (60.6)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; ISD, immunosuppressive drugs; RR: risk ratio; MP, methylprednisolone; CP, cyclophosphamide; DEX, dexamethasone; NA: not available.

Fig. 5. L’Abbé plot according to the treatment arm of retrospective studies. The seven retrospective studies of ISDs and PQ poisoning are presented in an L’Abbé plot. With the increased mortality in the placebo group, the mortality in the ISD group decreased.

A retrospective observational study conducted on patients with herbicide poisoning admitted to the emergency ward of the tertiary care hospital in South India between January 2004-2012 by Harika Cherukuri et al. showed that poisoning with herbicides is associated with high morbidity and mortality, and treatment with N-acetylcysteine, vitamin C, vitamin E, CP, hemodialysis and hemoperfusion may be useful in the reduction of the high mortality rate (Cherukuri et al., 2014). Other studies evaluated the effectiveness of the «Caribbean scheme» (CP, DEX, furosemide and vitamins B and C) drew a conclusion that it was associated with a lesser mortality rate in
Fig. 6. Risk of bias of four RCTs and two prospective studies.
the subjects who ingested ≤ 45 mL of 20% PQ solution (Botella de Maglia and Belenguer Tarin, 2000). However, these two studies lacked a control group, so it was difficult to draw firm conclusions and therefore we excluded these two studies to ensure the credibility of our study. In some other observational studies, the study by Jie Gao et al. states that prolonged MP therapy after pulse treatment can reduce the mortality of moderate-to-severe PQ poisoning patients (Gao et al., 2017). Early hemoperfusion may improve the survival chances of PQ poisoning patients, as was confirmed in three studies (Gao et al., 2015; Hsu et al., 2012; Wang et al., 2017). A multivariate logistic regression analysis showed that the addition of vitamin C to the treatment was significantly associated with increased survival of the patients in the study by Moon and Chun (2011). A CP dose was assessed in Sun and Lee’s study (2013). Though these studies were not related to the immediate goals of our study, they show a likely benefit of ISDs in PQ poisoning patients. Also, it is worth mentioning that a large number of case reports suggested that immunosuppressive therapy was beneficial to patients with moderate to severe PQ poisoning. Seven cases of necrosis of the femoral head after acute PQ poisoning were reported and in two studies patients were treated with glucocorticoid and CP. This should be administered cautiously in PQ poisoning patients (Tian et al., 2010; Wang et al., 2013). Although there is no convincing evidence for toxicity from ISDs in humans, our meta-analysis indicated that ISDs may reduce the mortality and incidence of MODS in patients with PQ poisoning. To make our conclusion more convincing and reduce obvious biases, we included more clinical studies and separated out the RCTs from the retrospective studies. The association of ISDs to reduce the incidence rate of MODS was not found in any other previous meta-analysis studies. Patients’ decreased mortality rates were associated with ISDs with the reduced incidence rate of MODS maybe being one reason for this. MODS is a main aetiology of death in these patients (Afzali and Gholyaf, 2008) and is associated with a PQ-induced organ injury mechanism that involves various reactive oxygen species produced from the PQ active human immune system and induced a variety of inflammatory cytokines (Gawarammana and Buckley, 2011; Sun and Lee, 2013). ISDs can reduce the incidence rate of MODS indirectly by reducing the production of inflammatory cytokines. The possible explanation for high heterogeneity regarding the effect of ISDs on patient’s mortality was that the type of drugs used was different. Of these five studies, two used CP, MP, and DEX, two used CP and MP, one combined CP and DEX.

Our meta-analysis has limitations. Firstly, the sample size of the included studies was small. Compared with other system reviews and meta-analysis, we included the most studies in our meta-analysis, and in order to make up the disadvantages, results of the pooled data from the retrospective study were used to prove our findings on RCTs, which may support our results to some extent. Secondly, the type of drug used was different; two studies did not use MP that belongs to the ISD group and three did not use DEX, hence we conducted subgroup analysis to avoid possible bias and find more believable results. Thirdly, the severity of the illness was not consistent across the studies. Patients in four RCTs suffered moderate to severe PQ poisoning, which may be due to the measuring error in plasma or urine PQ tests, hence we have drawn an L’Abbé plot, the result showing a possible advantage of ISDs in most of the patients with severe PQ poisoning.

In conclusion, the present meta-analysis study indicated that immunosuppressive therapy may reduce the mortality and incidence rate of MODS in patients with moderate to severe PQ poisoning. Severe PQ poisoning patients may benefit more from ISDs. Our study suggests that immunosuppressive treatment was not associated with an increased incidence of hepatitis and reduced incidence of ARF, and hypoxia. More research is needed to confirm this result.

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Conflict of interest—- The authors declare that there is no conflict of interest.

REFERENCES


