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Efficacy and safety of pulse immunosuppressive therapy with glucocorticoid and cyclophosphamide in patients with paraquat poisoning: A meta-analysis

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ABSTRACT

Purpose: Paraquat (PQ) is widely used in developing countries. Accidental or suicidal PQ poisoning is a public health concern due to lack of effective treatment. Because the role of pulse immunosuppressive therapy with glucocorticoid and cyclophosphamide for PQ poisoning is uncertain, we performed a meta-analysis to investigate the efficacy and safety of the therapy.

Method: A systematic literature search for randomized controlled trials (RCTs) and other clinical studies was performed in Pub Med, Embase, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature and Retrieval System, and Chinese Medical Current Contents. We estimated pooled relative risk ratios (RRs) and 95% confidence intervals (CIs) using a fixed effect model or random effect model. Outcomes included mortality, incidence of acute renal failure (ARF) and hypoxia, and leucopenia.

Results: Five studies (three RCTs) involving 332 PQ poisoning patients met the criteria. The mortality of moderate to fulminant poisoning patients receiving the pulse therapy was lower than that of the controls (60.4% vs. 85.3%; RR 0.71, 95% CI: 0.59, 0.86, $P = 0.0004$). The therapy also reduced the mortality of patients with moderate to severe PQ poisoning (45.1% vs. 79.1%, RR 0.45; 95% CI: 0.28, 0.75, $P = 0.002$). However, the therapy did not decrease the incidence of ARF and hypoxia. In addition, the pulse therapy caused more leucopenia than the controls (36.9% vs. 2.6%; RR: 9.12; 95% CI: 3.65, 22.81, $P < 0.00001$).

Conclusion: Pulse immunosuppressive therapy with glucocorticoid and cyclophosphamide may reduce the mortality of PQ poisoning patients, although the therapy may cause leucopenia.

1. Introduction

Paraquat (PQ), 1,1′-dimethyl-4, 4′-bipyridium dichloride, is one of the most widely used herbicides in developing countries. Suicide by PQ poisoning is a public health concern and the annual number of mortalities is as high as 300,000 in the Asia-Pacific region alone [1,2]. The causes of mortality from PQ poisoning are lung fibrosis related respiratory failure, which occurs only a few days or a few weeks after poisoning with moderate to severe toxicity, and multiple organ failure including acute respiratory distress syndrome (ARDS) and cardiac, hepatic and renal failures, which may develop within several hours to a few days after acute fulminant toxicity [3]. The lethal toxicity of PQ has resulted in a high mortality rate of 60–80%, which has been attributed to PQ's inherent toxicity and the lack of any effective treatment to ameliorate the toxic effects of poisoning [4].

Inflammation appears to constitute an early response of the PQ poisoning. Thus, blocking the inflammation process may inhibit the possibly lethal effects of PQ. In this context, immunosuppressive therapy is widely practiced as a treatment of PQ poisoning, especially pulse immunosuppressive therapy with glucocorticoid and cyclophosphamide [5].

However, clinical evidence of the efficacy remains limited and the safety of pulse therapy is less clear. We therefore undertook a meta-analysis of studies (both randomized and non-randomized controlled trials) to evaluate the efficacy and safety of pulse therapy with glucocorticoid and cyclophosphamide in PQ poisoning.

2. Methods

2.1. Search strategy

Eligible literature published before the end of June 2014 was identified through a search of PubMed, EMBASE and Chinese National Knowledge Infrastructure, Chinese Biomedical Literature and Retrieval System and Chinese Medical Current Contents. Search term combinations were as follows: paraquat, paraquat poisoning, immunosuppressive therapy, glucocorticoids, methylprednisolone, hydrocortisone, dexamethasone, cyclophosphamide and pulse therapy. All reference lists from the main reports and relevant reviews were hand searched for additional eligible

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studies. If any of these data was not available in the publications, further information was sought by correspondence with the authors.

2.2. Inclusion and exclusion criteria

Eligible studies should meet all of the following criteria: (1) prospective and/or retrospective studies, regardless of randomized controlled trials (RCTs); (2) study population included patients with PQ poisoning, who had orally ingested PQ; (3) patients in study group received pulse immunosuppressive therapy with glucocorticoids and cyclophosphamide; (4) the patients in control group not receiving pulse immunosuppressive therapy with glucocorticoids and cyclophosphamide; and (5) one or more of the efficacy outcomes reported: mortality rate, the incidence of acute renal failure (ARF) and hypoxia, respectively. In addition, leucopenia was used to estimate the safety outcome of the pulse immunosuppressive therapy. We excluded reviews, case reports, letters, editorials and studies without control groups or with full data not available.

2.3. Data extraction

Two authors (Peng Xu and Yao Liu) separately extracted data on study design, study quality, efficacy and safety outcomes. If there was any problem with a study, a third researcher (Jun Wang) further examined the study for inclusion. Data extracted included basic characteristics (first author, publication year, area, total number of patients, study design, illness severity/predicting methods, diagnostic criteria of ARF and hypoxia, follow-up) and definition of therapy in the study and control group. The main outcome was the mortality. The secondary outcomes included the incidence of ARF and hypoxia. The main complication was leucopenia. Extracted data were entered into a standardized Excel file. Any disagreements were resolved by discussion and consensus.

2.4. Assessment of methodological quality

Randomized studies were appraised using the Jadad score (0 = worst and 5 = best) [6]. This method assesses the adequacy of randomization, blinding, and the handling of withdrawals and dropouts; low quality studies have a score of ≤ 2 and high quality studies have a score of ≥ 3. In addition, the Newcastle-Ottawa Scale (NOS) [7] was used to evaluate two non-RCTs and the selection, comparability and overall outcomes for the studies. The maximum NOS score was 9, and the studies with ≥ 6 were considered to be of higher quality.

2.5. Statistical analysis

All statistical analyses were performed with Review Manager (version 5.3 Cochrane Collaboration, Oxford, UK). All dichotomous outcomes were expressed as the risk ratio (RR) and relevant 95% confidence intervals (CIs) and mean differences (MDs) with 95% CIs for continuous outcomes. Heterogeneity across trials was evaluated with the I^2 statistics. I^2 values ranged from 0% to 100%, in which 0%, 25–49%, 50–74%, and $\geq 75\%$ suggested no, low, moderate, and high heterogeneity, respectively [8]. An I^2 value $>50\%$ and a P-value <0.1 were defined as significant heterogeneity in the meta-analysis. A fixed-effect model or random-effect model was used, depending on the absence or presence of heterogeneity. When heterogeneity existed, a random effect model was used to assess the overall estimate, otherwise, a fixed effect model was chosen. Subgroup and sensitivity analyses were performed to account for heterogeneity. The analyses were used to explore differences in study designs, therapeutic methods, illness severity, and other confounding factors among trials that might be expected to alter the magnitude of treatment effect. The number of studies included is too small to examine using funnel plots to detect reporting bias.

3. Results

3.1. Study selection

Our search identified 2418 potentially eligible citations as shown in Fig. 1. After scanning titles and abstracts, 2364 citations were excluded and 54 were retained for further evaluation. We retrieved 54 citations for detailed evaluation, of which 49 were excluded. Five studies [4, 9–12], which included three RCTs and two non-RCTs, met the inclusion criteria. All these studies were written in English.

3.2. Characteristics and methodological quality of the studies

The basic characteristics of studies included in meta-analysis were reported in Table 1. The five trials enrolled 332 patients, and the datasets utilized were first author/publication year, area, total number of patients, study design, illness severity/predicting methods, diagnostic criteria of ARF and hypoxia, follow-up and the definition of therapy in study group and control group. Patients in two trials used repeat pulse therapy and patients in three other trials used non-repeat. Three trials used urine PQ tests only, and two other trials used urine qualitative PQ tests and plasma quantification PQ tests. Three trials used cyclophosphamide infusion for 2 days and methylprednisolone infusion for 3 days simultaneously preceding dexamethasone treatment. Two trials did not precede dexamethasone.

The quality assessment of RCTs is shown in Table 3. Two of all RCTs described the special method of randomization, such as according to random digit methods [10] or by means of a sequence of labeled cards contained in sealed numbered envelopes [4]. All RCTs described the main outcome at final follow-up in full. However, double blinding was impossible in all RCTs. In addition, the scores of NOS scale for the remainder 2 non-RCTs were 6 [12] and 5 [9] respectively.

3.3. The main outcome: mortality

For the data in Fig. 2, 60.4% (102/169) patients died in the "pulse therapy" group while 85.3% (139/163) patients died in the control group; the aggregated results of these studies suggest that the use of pulse immunosuppressive therapy reduced the mortality of patients with PQ moderate to fulminant poisoning (RR, 0.71; 95% CI: 0.59,

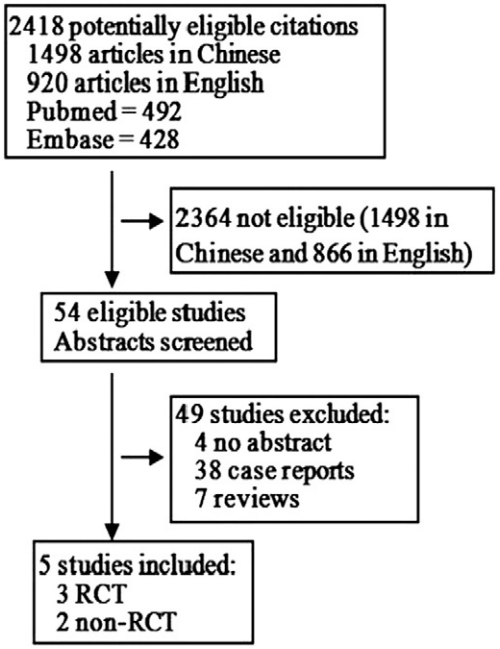

Fig. 1. Literature search strategy.