Immunosuppressive therapy in lung injury due to paraquat poisoning: a meta-analysis

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ABSTRACT

__Introduction:__ Immunosuppressive therapy has been shown to improve outcomes in patients with paraquat poisoning. The objective of this study was to evaluate the efficacy of immunosuppressive therapy in the management of lung injury due to paraquat poisoning.

__Methods:__ We searched the MEDLINE, OVID, and CINAHL databases for relevant studies published from 1980 to 2006. We included studies if (a) the study design was a randomised controlled trial, observational study with historical controls or observational study; (b) the study population included patients with paraquat poisoning, and received immunosuppressive therapy; and (c) the study provided data on mortality. We calculated the survival rate with 95 percent confidence intervals (CI) for observational studies, and relative risk and 95 percent CI for dichotomous outcomes.

__Results:__ 12 studies - four non-randomised, six non-randomised comparing historical controls, and two randomised controlled trials - had employed immunosuppressive therapy in the management of paraquat poisoning. The survival rate in the four non-randomised studies (39 patients) was 74.4 percent (95 percent CI 58.9-85.4). The relative risk of immunosuppressive therapy in decreasing mortality with paraquat poisoning was 0.55 (95 percent CI 0.39-0.77) and 0.6 (95 percent CI 0.27-1.34) for the non-randomised studies (comparing historical controls) and randomised controlled studies, respectively. There was significant heterogeneity and evidence of publication bias.

__Conclusion:__ One out of four patients (95 percent CI 3-5) were successfully treated with immunosuppressive therapy for paraquat poisoning. However, due to significant heterogeneity and publication bias, a large randomised controlled trial will be required to affirm the role of immunosuppression in paraquat poisoning.

__Keywords:__ cyclophosphamide, glucocorticoids, immunosuppressive therapy, lung injury, paraquat poisoning

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INTRODUCTION

Poisoning by pesticides and other agricultural chemicals is a major public health problem worldwide, especially in the developing countries. Paraquat, a widely-used herbicide, remains a major cause of suicidal death in many countries, such as Pakistan and Sri Lanka.[1] In fact, there are about 20,000 annual fatalities and more than two million hospitalisations due to poisoning by pesticides and other agricultural chemicals.[2] More than 200 deaths were reported in the first two decades after its widespread use began in 1958.[3]

Paraquat is highly toxic and causes damage to the lungs, liver and kidneys. Paraquat poisoning can be classified into three categories: (1) patients with mild poisoning (20 mg paraquat ion per kg of body weight) have minor gastrointestinal symptoms but usually fully recover; (2) severe poisoning (20–40 mg paraquat ion per kg of body weight) in which the patients develop acute renal failure, acute lung injury and progressive pulmonary fibrosis with death occurring in 2–3 weeks from respiratory failure; and (3) fulminant poisoning (40 mg paraquat ion per kg of body weight) in which the patients develop multiple organ failure leading to death within hours to a few days after ingestion.[4]

Paraquat concentration in the lung parenchyma is 10–20 times greater than in plasma because of active, energy-dependent uptake of paraquat by type 1 and type 2 pneumocytes via the polyamine uptake pathway.[5] Death from severe paraquat poisoning primarily results from progressive pulmonary damage secondary to diffuse alveolar damage with resultant acute respiratory distress syndrome.[6] The cytotoxic effects of paraquat have been

attributed to the generation of superoxide radicals after reduction of paraquat by intracellular oxidases; amplified generation of reactive oxygen species further results in profound pulmonary injury. The results of treatment for paraquat poisoning, including absorbents, pharmacological approaches,[7] radiotherapy,[8] haemodialysis and haemoperfusion[9] were disappointing. In this context, the use of immunosuppressive therapy (combination of glucocorticoids and cyclophosphamide) has been shown to be a promising alternative. Immunosuppressive therapy is not warranted in mild poisoning, while patients with fulminant poisoning generally die before the therapy takes effect. Thus, it is the patients in the severe group (those with lung injury) who would generally benefit from immunosuppressive therapy.[4] A systematic review performed in 2003 did not find good evidence of benefit or harm from immunosuppression. However, the authors had not used the meta-analytical approach in that systematic review.[10] In this study, we systematically evaluated the role of immunosuppressive therapy in the management of lung injury due to paraquat poisoning using a meta-analytical approach.

METHODS

We searched the electronic databases—MEDLINE, OVID and CINAHL using the key word "paraquat poisoning"—limiting the search by age ($\geq$ 19 years) and duration (1980–2006). We included both randomised controlled trials and non-randomised studies. Bibliographies of all selected articles and review articles that included information on paraquat poisoning were reviewed for other relevant articles. In addition, we reviewed our personal files. All the studies, irrespective of language, were identified.

Two authors (RA and RS) independently reviewed the abstracts of the studies, without blinding, to study the details. Any disagreement was resolved by discussion between the authors. Data was recorded on a standard data extraction form. The following criteria were used to select articles: (a) study design was a randomised controlled trial, non-randomised study with or without historical controls; (b) study population included patients with paraquat poisoning, and who received immunosuppressive therapy with glucocorticoids and cyclophosphamide (the control group was managed with supportive care alone); and (c) the study provided data on mortality. We individually analysed randomised controlled trials, non-randomised studies that included historical controls and non-randomised studies without historical controls.

The methodological quality of each trial was evaluated using the five-point scale (0 = worst and 5 = best) as described by Jadad et al.[11,12] This instrument assesses the adequacy of randomisation, blinding, and the handling of withdrawals and dropouts; low quality studies have a score of $\leq$ 2 and high quality studies a score of $\geq$ 3.[12,13] The statistical package StatsDirect version 2.5.7 for MS Windows (StatsDirect Ltd, Cambridge, England) was used to perform the statistical analysis.

For observational studies, we used binomial proportions to calculate the efficacy of immunosuppression in paraquat poisoning, in which the numerator was the survival rate, and denominator the total study population. The expected proportion was the success rate of each study included. We then calculated the 95% confidence intervals (CI) for the expected proportion using the Newcombe-Wilson method.[14,15] The data from individual studies was then pooled, and a summary success rate with 95% CI was calculated.

For controlled studies, we calculated the relative risk (RR) and 95% CI to assess the effect of immunosuppression in decreasing mortality in paraquat poisoning. The results from individual studies were pooled using the random effects model of DerSimonian and Laird.[16] We also calculated the number needed to treat (NNT = 1 / risk difference) with 95% CI. This numerical expression of results was used to estimate the number of patients with paraquat poisoning that need to be treated with immunosuppression to prevent one death. The extent of heterogeneity for mortality was assessed by the Cochran Q statistic (weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method). The p-value level at which heterogeneity should be diagnosed is unclear, given that the Q statistic has low power, and Fleiss has recommended a value of at least 0.1.[17]

The impact of heterogeneity upon the pooled estimates of the individual outcomes of the meta-analysis was assessed using the chi-square test and/or the I^2 tests (measures the extent of inconsistency among the results of the studies, and is interpreted as approximately the proportion of total variation in study estimates that is due to heterogeneity, rather than sampling error). An I^2 value of more than 50% indicates significant heterogeneity. As the chi-square test has a low sensitivity for detecting heterogeneity, a p-value of less than 0.1 was considered significant for the presence of statistical heterogeneity.[18] Finally, visual inspection of the Forest plots was also used to qualitatively assess heterogeneity. For the observational study meta-analysis, heterogeneity could be assessed only qualitatively by visual inspection of the Forest plot, because of the study design of abstract patient data and observational data.[19]

We checked for the presence of publication bias using the Begg's funnel plot.[20] The funnel plot is a measure of the log of the RR (in the x-axis, a measure of diagnostic
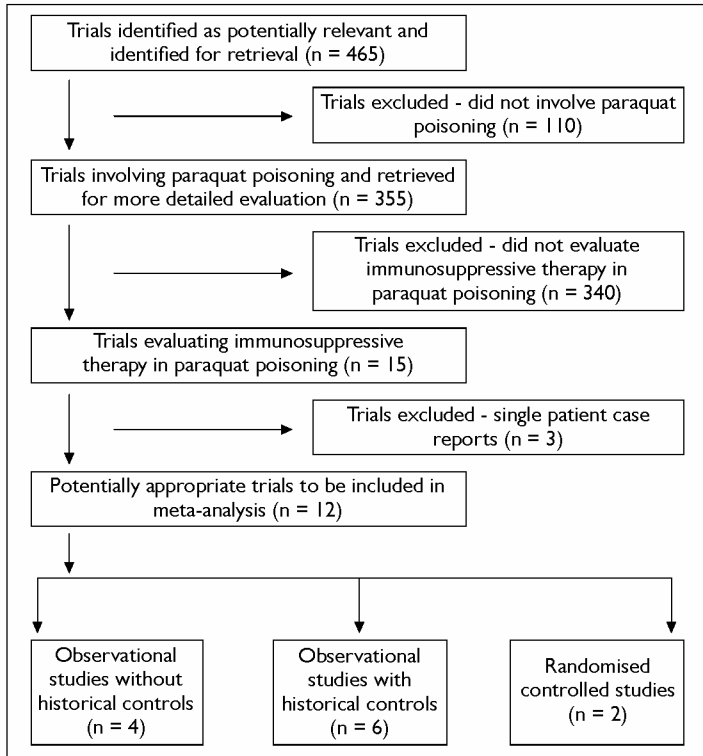
Fig. 1 Flow diagram shows the trial selection process for this meta-analysis.
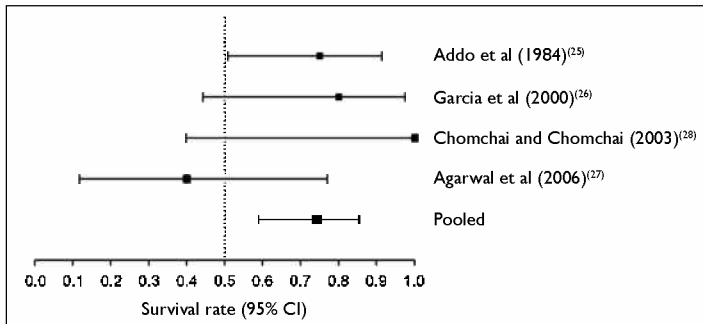

Fig. 2 Forest plot shows the success rate of immunosuppressive therapy in paraquat poisoning with 95% confidence intervals.
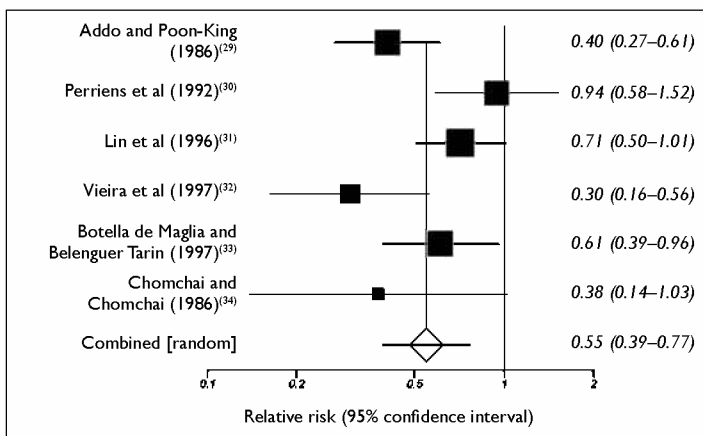

Fig. 3 Forest plot shows that immunosuppressive therapy significantly decreases hospital mortality in patients with paraquat poisoning in the non-randomised studies with historical controls.

accuracy) against the standard error of the log of the RR (in the y-axis, an indicator of sample size). Each open circle represents each study in the meta-analysis. The vertical line in the centre indicates the summary RR and the other two lines indicate the 95% CI. In the absence of publication bias, the RR estimates from smaller studies are expected to be scattered above and below the summary estimate, producing a triangular or funnel shape. Institutional review board clearance was not required for this manuscript as this was a meta-analysis of published studies.

RESULTS

Our initial electronic searches yielded 465 citations (Fig. 1). Of these, 110 studies were excluded as they did not involve paraquat poisoning; 340 trials were further excluded as they involved paraquat poisoning but not immunosuppressive therapy. One trial had used glucocorticoids alone (intravenous hydrocortisone 100 mg every six hours).[21] Fifteen trials had utilised immunosuppressive therapy with glucocorticoids and cyclophosphamide. However three trials were single patient case reports and were also excluded.[22-24] Finally, 12 trials were included for data analysis: four were observational studies,[25-28] six were observational studies but had employed historical controls,[29-34] and two were randomised controlled trials.[35,36] All studies provided data on mortality.

Of the non-randomised studies (without historical controls) (Table I), three were fully published,[25-27] and one was reported as an Abstract.[28] Because of the observational nature, the Jadad score was zero for all the studies. The four observational studies without controls included a total of 39 patients, of which 29 patients survived, giving a total survival rate of 74.4% (95% CI 58.9–85.4) (Fig. 2). Heterogeneity was noted by visual inspection of the Forest plots.
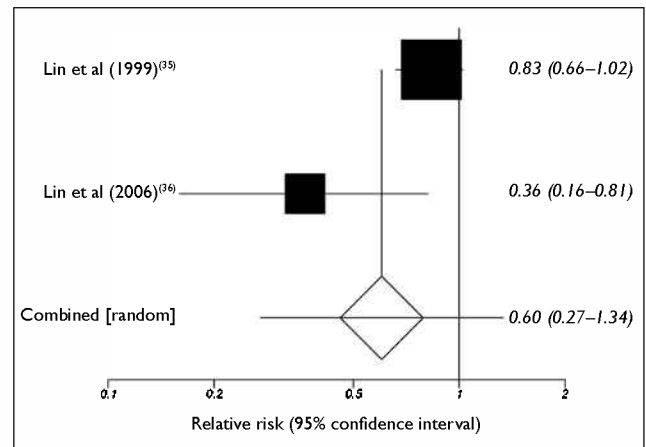

Fig. 4 Forest plot shows that immunosuppressive therapy decreases hospital mortality (although not statistically significant) in patients with paraquat poisoning in the randomised controlled trials.

Table I. Non-randomised studies utilising immunosuppression in paraquat poisoning.

Study	Immunosuppressive treatment	Survival, n (%)	Success rate (95% CI)
Addo et al (1984)[25]	Dexamethasone 8mg IV q 8h - 2 weeks, then 0.5 mg PO, q 8h - 2 weeks. Cyclophosphamide 1.66 mg/kg IV q 8h (maximum 4 g over 4 weeks).	15/20 (75)	80 (44.4–97.5)
Garcia et al (2000)[26]	Methylprednisolone 1g IV q 24h - 3 days. Dexamethasone 8mg IV q 8h - 7 days. Cyclophosphamide 1 g IV q 24h - 2 days.	8/10 (80)	75 (50.9–91.3)
Chomchai and Chomchai (2003)[28]	Dexamethasone 10 mg IV q 8h - 14 days. Cyclophosphamide 1.7 mg/kg IV q 8h - 14 days.	4/4 (100)	100 (39.8–100)
Agarwal et al (2006)[27]	Methylprednisolone 15 mg/kg q 24h - 3 days. Cyclophosphamide 10 mg/kg q 24h - 2 days, followed by Dexamethasone 4 mg IV q 8h until recovery or death.	2/5 (40)	40 (11.8–76.9)

Table II. Controlled studies utilising immunosuppression in paraquat poisoning.

Study	Immunosuppressive therapy	Mortality in experimental group, n/N (%)	Mortality in control group, n/N (%)
Non-randomised studies comparing historical controls			
Addo and Poon-King (1986)[29]	Dexamethasone 8mg IV q8h - 2 weeks, then 0.5 mg PO q 8h - 2 weeks. Cyclophosphamide 1.66 mg/kg IV q 8h (maximum 4 g over 4 weeks).	20/72 (27.8)	42/61 (68.9)
Perriens et al (1992)[30]	Dexamethasone 8 mg IV q 8h - 2 weeks, then 0.5 mg PO q 6h - 2 weeks. Cyclophosphamide 1.66 mg/kg IV q 8h (maximum 4 g or 2 weeks).	20/31 (64.5)	9/14 (64.3)
Lin et al (1996)[31]	Methylprednisolone 1 g IV q 24h - 3 days. Cyclophosphamide 1 g IV q 24h - 2 days.	17/29 (58.6)	23/28 (82.1)
Vieira et al (1997)[32]	Dexamethasone 1.5 mg/kg q 24h D1-4; 1 mg/kg q 24h D5-7; then 24 mg q 24h. Cyclophosphamide 15 mg/kg IV D1, 10 mg/kg D 2, 7 mg/kg D 3-5; 5 mg/kg q 24h until total dose of 4 g or leukocyte count < 3000/mm³.	7/25 (28)	10/10 (100)
Botella de Maglia and Belenguer Tarin (2000)[33]	Dexamethasone 8mg IV q 8h - 2 weeks, then 0.5 mg PO q 8h for 2 weeks. Cyclophosphamide 1.66 mg/kg IV q 8h (maximum 4 g over 4 weeks).	10/18 (55.6)	10/11 (90.9)
Chomchai and Chomchai (2004)[34]	Dexamethasone 0.15 mg/kg q 6h and cyclophosphamide 5 mg/kg q 24 h in divided doses for 14 days.	2/6 (33.3)	9/9 (100)
Randomised controlled trials			
Lin et al (1999)[35]	Methylprednisolone 1 g IV q 24h - 3 days. Dexamethasone 8mg IV q 8h - 2 weeks. Cyclophosphamide 15 mg/kg IV q 24h - 2 days.	38/56 (67.9)	53/65 (81.5)
Lin et al (2006)[36]	Methylprednisolone 1 g IV q 24h -3 days. Cyclophosphamide 15 mg/kg IV q 24h - 2 days. Dexamethasone 20 mg q 24h until PaO_2 > 80 mmHg. Repeat doses of methylprednisolone 1 g IV q 24h -3 days and cyclophosphamide 15 mg/kg IV q 24h -1 day (if PaO_2 < 60 mmHg).	5/16 (31.3)	6/7 (85.7)

n: mortality number; N: total number

There were two randomised controlled trials and six non-randomised studies, that have compared the study group with historical controls (Table II). All studies were fully published, except for one study which was reported as an Abstract.[32] The Jadad score for the observational studies was zero. For the two randomised controlled studies, the Jadad score was one[35] and three.[36] The total numbers of patients after combining the six non-randomised studies and two randomised controlled trials were 316 and 144, respectively (Table II). The relative risk of immunosuppressive therapy in decreasing mortality with paraquat poisoning was 0.55 (95% CI 0.39–0.77) and 0.6 (95%CI 0.27–1.34) for the observational studies (comparing historical controls) (Fig. 3) and randomised controlled studies (Fig. 4), respectively. Combining both the groups, one out of four patients (95 percent CI 3–5) were successfully treated with immunosuppressive therapy for paraquat poisoning (NNT 3 [95% CI 3–4] and 5 [95% CI 3–14] for observational studies and randomised trials, respectively).

There was significant clinical heterogeneity as evidenced by different patient populations, doses administered and methods used for diagnosis. There was significant heterogeneity detected by the three statistical tests for the observational studies with historical controls (Cochran Q statistic 22.14, p = 0.001; I^2 statistic 72.9%; chi-square statistic 40.5, p < 0.001). However, for the randomised trials, the Cochran Q statistic indicated heterogeneity (Cochran Q statistic 4.0, p = 0.045) but was not observed with the chi-square test (chi-square statistic 1.56, p = 0.21).The funnel plots showed evidence of significant publication bias for the outcome of mortality in all the controlled studies (Fig.5).
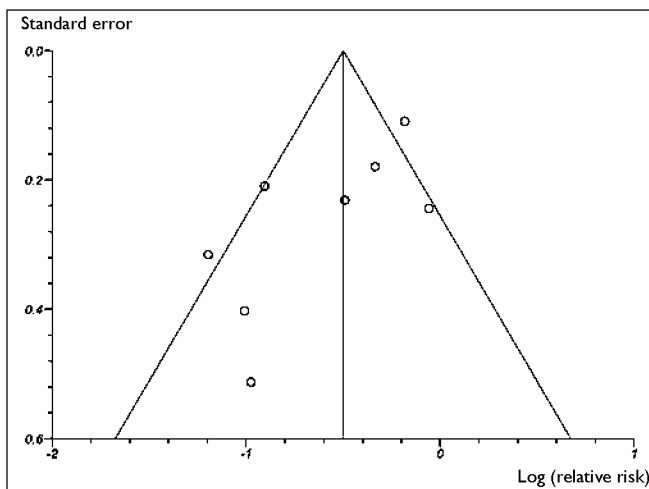

Fig. 5 Funnel plot compares log relative risk (RR) versus the standard error of log RR. Open circles represent trials included in the meta-analysis. The vertical line in the centre indicates the summary log RR. The other lines represent the 95% CIs. Asymmetry about the pooled RR line is consistent with the presence of publication bias for the outcome of mortality in patients with paraquat poisoning treated with immunosuppressive therapy.

DISCUSSION

The result of our systematic review suggests that immunosuppressive therapy with glucocorticoids and cyclophosphamide is efficacious in the management of lung injury in patients with severe paraquat poisoning, and is likely to decrease the mortality in this group of patients. However, this conclusion has limitations in that there is significant methodological heterogeneity (different patient populations, varying time and doses of immunosuppressive drugs), and thus a large randomised controlled trial is required to confirm the role of immunosuppression in paraquat poisoning. In this regard, this meta-analysis shares the view of the previous systematic review. However, unlike the conclusions drawn from the previous systematic review, this study shows evidence of benefit with the use of immunosuppression in all forms of studies, and hence supports the use of immunosuppression in patients with severe paraquat poisoning.

The definite mechanism of this anti-inflammatory therapy has not been elucidated. However, it is known that severe inflammation as a result of paraquat poisoning is the prime factor in the pathogenesis of lung injury.[37] Glucocorticoids are potent anti-inflammatory agents. Moreover, pulse methylprednisolone has also been shown to suppress superoxide production by neutrophils and macrophages and the formation of superoxide in the arachidonic acid cascade.[38] This action is further potentiated by cyclophosphamide therapy, a broad spectrum immunomodulator, which influences virtually all components of cellular and humoral immune response and reduces the severity of inflammation.[39]

Meta-analysis is a statistical strategy for assembling the results of several studies into a single estimate. It provides a more precise estimate of a treatment effect, and may explain heterogeneity between the results of individual studies.[40] Although generally applied to randomised studies, a growing number of meta-analyses of observational studies (or non-randomised studies) in epidemiology (MOOSE) have appeared in the literature.[41,42] The limitations of non-randomised study designs are well known to researchers, yet in some areas of healthcare, the majority of evidence addressing the effectiveness of clinical interventions rests on non-randomised study designs. Although historical controls are generally accepted only if there are clearly defined statistical predictors of prognosis, which show that the two groups were comparable at baseline, we combined studies analysing historical controls with randomised controls because of the paucity of data. In fact, this is the basis on which N-acetyl cysteine has been accepted as an effective antidote for paracetamol poisoning.[43]

The major limitation of this meta-analysis is the presence of significant clinical, methodological and statistical heterogeneity, and publication bias. Thus, large, properly conducted, adequately powered, randomised controlled trials are required to settle the issue. Assuming a survival rate of 19% in the standard medical therapy group (seen in the two randomised controlled trials), and achieving a 10% better survival with immunosuppressive therapy, we would require 306 patients in each group to detect these differences (confidence level [1-α] 95%, power level [1-β] 80%). Although considerable effort would be required to recruit such a large group of patients, this meta-analysis would definitely strengthen the stand on the role of immunosuppression in paraquat poisoning.

In conclusion, the results of our meta-analysis suggest that immunosuppression with glucocorticoids and cyclophosphamide can decrease mortality related to paraquat poisoning. However due to significant heterogeneity and publication bias, a large randomised

controlled trial is required to affirm the role of immunosuppression in paraquat poisoning.

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