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Li, LR; Sydenham, E; Chaudhary, B; Beecher, D; You, C (2014)
Glucocorticoid with cyclophosphamide for paraquat-induced lung fi-
brosis. *Cochrane Database Syst Rev*, 8. CD008084. ISSN 1469-493X
DOI: <https://doi.org/10.1002/14651858.CD008084.pub4>

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Cochrane Database of Systematic Reviews 2014, Issue 8. Art. No.: CD008084.
DOI: 10.1002/14651858.CD008084.pub4.

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[Intervention Review]

Glucocorticoid with cyclophosphamide for paraquat-induced lung fibrosis

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Editorial group: Cochrane Injuries Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2014.

Review content assessed as up-to-date: 15 April 2014.

Citation: Li LR, Sydenham E, Chaudhary B, Beecher D, You C. Glucocorticoid with cyclophosphamide for paraquat-induced lung fibrosis. *Cochrane Database of Systematic Reviews* 2014, Issue 8. Art. No.: CD008084. DOI: 10.1002/14651858.CD008084.pub4.

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ABSTRACT

Background

Paraquat is an effective and widely used herbicide but is also a lethal poison. In many developing countries paraquat is widely available and inexpensive, making poisoning prevention difficult. However most of the people who become poisoned from paraquat have taken it as a means of suicide.

Standard treatment for paraquat poisoning both prevents further absorption and reduces the load of paraquat in the blood through haemoperfusion or haemodialysis. The effectiveness of standard treatments is extremely limited.

The immune system plays an important role in exacerbating paraquat-induced lung fibrosis. Immunosuppressive treatment using glucocorticoid and cyclophosphamide in combination is being developed and studied.

Objectives

To assess the effects of glucocorticoid with cyclophosphamide on mortality in patients with paraquat-induced lung fibrosis.

Search methods

The most recent search was run on the 15th April 2014. We searched the Cochrane Injuries Group's Specialised Register, The Cochrane Library, Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R), Embase Classic+Embase (Ovid), ISI WOS (SCI-EXPANDED, SSCI, CPCI-S & CPSI-SSH), trials registries, Chinese databases (数据库, 万方数据库, 维普数据库) and reference lists.

Selection criteria

RCTs were included in this review. All patients were to receive standard care, plus the intervention or control. The intervention was glucocorticoid with cyclophosphamide in combination versus a control of a placebo, standard care alone or any other therapy in addition to standard care.

Data collection and analysis

The mortality risk ratio (RR) and 95% confidence interval (CI) was calculated for each study on an intention-to-treat basis. Data for all-cause mortality at final follow-up were summarised in a meta-analysis using a fixed-effect model.

Main results

This systematic review includes three trials with a combined total of 164 participants who had moderate to severe paraquat poisoning. Patients who received glucocorticoid with cyclophosphamide in addition to standard care had a lower risk of death at final follow-up than those receiving standard care only (RR 0.72; 95% CI 0.59 to 0.89).

Authors' conclusions

Based on the findings of three small RCTs of moderate to severely poisoned patients, glucocorticoid with cyclophosphamide in addition to standard care may be a beneficial treatment for patients with paraquat-induced lung fibrosis. To enable further study of the effects of glucocorticoid with cyclophosphamide for patients with moderate to severe paraquat poisoning, hospitals may provide this treatment as part of an RCT with allocation concealment.

PLAIN LANGUAGE SUMMARY

Using steroids and cyclophosphamide together as a treatment for paraquat poisoning

Paraquat is an effective and widely used herbicide but is also a lethal poison. In many developing countries paraquat is widely available and inexpensive, making poisoning prevention difficult. However most of the people who become poisoned from paraquat have taken it as a means of suicide.

Standard care for removing paraquat from the body involves vomiting, consuming activated charcoal or Fuller's Earth (which absorbs paraquat), and blood filtering. This review aims to assess the effects of giving patients steroids and cyclophosphamide in addition to standard care to prevent death after paraquat poisoning.

We found three small randomised controlled trials in which patients with moderate or severe poisoning were given either standard care only or standard care and steroids and cyclophosphamide. When the results of the three studies were combined, we found that patients who were given standard care and steroids and cyclophosphamide had a reduced risk of death of about 28% (statistically estimated likely range of reduced deaths from 41% to 11%) compared with patients given standard care alone. However, the studies were small and one was of low methodological quality so the benefit of this treatment should be interpreted with caution. To understand the effects of this treatment for poisoned patients better, we recommend it be given in the context of a randomised controlled trial so that future results can be analysed with similar studies.

BACKGROUND

Paraquat is one of the most widely used herbicides worldwide. It is commercially produced and has been sold in around 130 countries since 1961, despite its fatal toxicity to humans (Tomlin 1994). Because it is inexpensive and widely available, it is difficult to prevent paraquat poisoning. Paraquat poisoning by accidental or voluntary ingestion accounts for numerous deaths each year, predominantly in developing countries where its use is less stringently controlled than in Europe or the US.

An epidemiological study of poisoning in rural Sri Lanka found an incidence of poisoning of 75 per 100,000 population, with a death rate of 22 per 100,000 population. The incidence and death rates from poisoning were highest in the 15 to 34 years age group, and there were significant differences in the incidence of

poisoning among different ethnic groups. In this study, paraquat was the most common poisoning agent (Hettiarachchi 1989).

In China, paraquat poisoned patients are usually women and children in impoverished rural areas, who have received a low standard of education and are often unfairly treated. In many cases, the decision to drink paraquat is impulsive and follows an intense interpersonal conflict (Wang 2008).

Description of the condition

The prognosis in paraquat poisoning is associated with the amount of toxin ingested.

- In low-dose poisoning (< 20 mg of paraquat ion per kg of body weight) patients are often asymptomatic, or may develop vomiting or diarrhoea, but have a good chance of recovery.
- In moderate-dose poisoning (20 mg to 40 mg of paraquat ion per kg of body weight), initial renal and hepatic dysfunction is common. Mucosal damage may become apparent with sloughing of the mucous membranes in the mouth. Difficulty in breathing may develop after a few days in more severe cases. After about 10 days, although renal function often returns to normal, radiological signs of lung damage usually develop. Lung damage is usually followed by irreversible massive pulmonary fibrosis manifested by the progressive loss of the lungs' ability to breathe, and deterioration continues until the patient eventually dies, between two and four weeks after ingestion.
- In high-dose poisoning (> 40 mg paraquat ion per kg of body weight), toxicity is much more severe and death occurs early (within 24–48 h) from multiple organ failure. Vomiting and diarrhoea are severe, with considerable fluid loss. Renal failure, cardiac arrhythmias, coma, convulsions and oesophageal perforation leads to death (WHO 2009).

Description of the intervention

The care of a paraquat poisoned person involves reducing the quantity of paraquat ingested and removing paraquat from the bloodstream. Vomiting should be induced as soon as possible to prevent further absorption of the toxin (Dinham 1996). Upon arrival at the emergency department, further interventions may include gastric aspiration, gastric lavage, repeated administration of the absorbents activated charcoal or Fuller's Earth, and purgatives such as mannitol or sorbitol (WHO 2009). Haemodialysis, haemofiltration, and haemoperfusion can be instituted with the aim of reducing the load of poison in the blood, but these interventions have no confirmed effects for improving survival (Suzuki 1993; Koo 2002), mainly because paraquat accumulates in the lungs.

Paraquat molecules selectively accumulate in the lungs, leading to irreversible pulmonary fibrosis, which is also known as 'paraquat lung' (Smith 1975; Fukuda 1985). This accumulation process begins immediately after ingestion and lasts from two to four weeks. A large proportion of patients appear asymptomatic until signs of breathing difficulty emerge; it is difficult to predict the outcome of a patient who appears normal but is actually suffering lung fibrosis (Eddleston 2003).

While numerous methods are available to reduce paraquat concentration in the bloodstream, the progression of lung injury through the deposited paraquat is a major concern. Using glucocorticoid and cyclophosphamide in combination as a means of suppressing the immunoreactions that cause lung damage has been tested since the 1970s (Eddleston 2003), but the effectiveness of this treatment is unknown. The timing of providing treatment, the

duration of treatment and the dosage of drugs can vary depending on the needs of the patient.

How the intervention might work

After being actively accumulated by lung cells, paraquat catalyses the formation of certain chemicals, namely superoxide, singlet oxygen, hydroxyl and peroxide radicals. These chemicals are also used by the immune system as 'weapons' to destroy items recognised as foreign to the human body (Smith 1988). It is believed that immunosuppressive methods prevent the immune system from producing such chemicals thereby reducing damage. At the same time, the immunosuppressive agents are intended to halt the progress of fibrosis, which is a part of immune reaction (Jaeschke 1997).

Why it is important to do this review

Though it has been inferred from experimental (Lee 1984) and clinical experience (Agarwal 2006) that immunosuppressive therapy might reduce deaths among paraquat poisoned patients, there has been no conclusion on the effectiveness of this treatment. Considering the hazards associated with immunosuppressive drugs (Winsett 2004), for example by making patients more prone to infection in the long term, it is timely to have a systematic review on this topic to support decision-making or suggest further research.

OBJECTIVES

To assess the effects of glucocorticoid with cyclophosphamide on mortality in patients with paraquat-induced lung fibrosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were included.

Types of participants

Any person with paraquat poisoning.

Types of interventions

All patients were to receive standard care plus either the intervention or control.

- Intervention: glucocorticoid with cyclophosphamide in combination.
- Control: placebo, standard care alone or any other therapy in addition to standard care.

Studies that focused on any single immunosuppressant or other combinations of therapies were excluded.

Types of outcome measures

- Mortality at 30 days following the ingestion of paraquat.
- All-cause mortality at the end of the follow-up period.

Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status.

Search strategies with notes for this update are listed in [Appendix 1](#). Search methods and strategies for previous versions of the review can be found in [Appendix 2](#).

Electronic searches

The Cochrane Injuries Group's Trials Search Co-ordinator searched the following:

1. Cochrane Injuries Group specialised register (15th April 2014);
2. Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*) (issue 4 of 12, 2014);
3. Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to 15th April 2014);
4. Embase Classic + Embase (OvidSP) (1947 to 15th April 2014);
5. ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to April 2014);
6. ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to April 2014);
7. Clinicaltrials.gov (www.clinicaltrials.gov) (accessed 15th April 2014);
8. Current Controlled Trials (<http://www.controlled-trials.com/>) (15th April 2014);
9. International Clinical Trials Registry Platform <http://apps.who.int/trialsearch/> (15th April 2014).

The following Chinese databases were searched by the authors (LL):

- China National Knowledge Infrastructure (CNKI 数据库) (May 2014),

- WAN FANG DATA (万方数据库) (May 2014),
- VIP (维普数据库) (May 2014).

Searching other resources

We searched the Internet through search engines [Google.com](http://www.google.com) and [Baidu.com](http://www.baidu.com), using the term 'clinical trial & paraquat'. We also checked the reference lists of reports and literature reviews on paraquat poisoning for potentially relevant published or unpublished trials. We contacted the authors of the included trials for further information.

Data collection and analysis

Selection of studies

The search results from English language databases were screened independently by LL, BC, DB and ES. The results from the Chinese databases were screened independently by LL and YC. The full-text versions of potentially relevant trials were obtained and assessed. Duplicate reports were identified and noted. LL and BC disagreed about the inclusion of the [Afzali 2008](#) study due to the use of alternation as the method of randomisation. YC moderated the discussion on inclusion of this trial, and it was agreed that the trial would be included but noted as being of high risk of bias.

Data extraction and management

Data from the three included trials were extracted independently by LL, BC and ES. Data were extracted on the study design, number of participants in the intervention and control groups, the number of deaths in each group on an intention-to-treat basis, and loss to follow-up in each trial. Information on the methodology of each trial was recorded for assessment of the risk of bias, as described below. Data were analysed using Review Manager software ([RevMan 2011](#)).

Assessment of risk of bias in included studies

Three review authors (LL, BC and ES) independently evaluated the risk of bias for each included trial in the following domains: sequence generation, allocation concealment, blinding, incomplete reporting, selective outcome reporting and any other sources of bias. To facilitate a valid judgement, we wrote to the contact person of each trial to request further information. Our judgement was made according to the criteria defined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), with an assessment of 'low risk of bias' or 'high risk of bias' made for each criteria. 'Unclear risk of bias' indicates that not enough information was provided for us to make a judgement on

a particular area of bias. The judgements can be found in the 'Risk of bias' tables below, and a summary of the judgements are given in [Figure 1](#) and [Figure 2](#).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies. Three studies are included in this review.

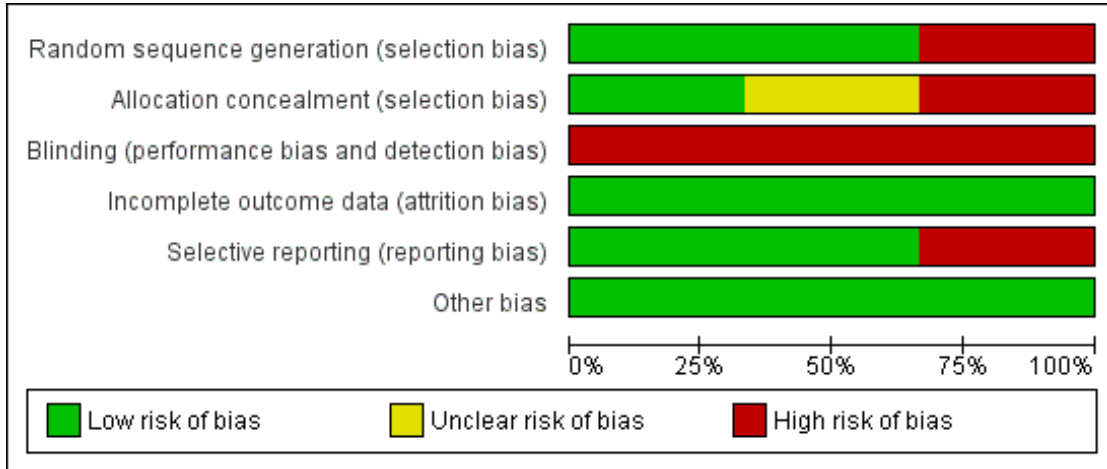


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Afzali 2008	-	-	-	+	+	+
Lin 1999	+	?	-	+	-	+
Lin 2006	+	+	-	+	+	+

Measures of treatment effect

The risk ratio (RR) and 95% confidence interval (CI) was calculated for each trial on an intention-to-treat basis. Data for all-cause mortality at final follow-up were summarised in a meta-analysis using a fixed-effect model.

Dealing with missing data

The amount of loss to follow-up in each trial was assessed.

Assessment of heterogeneity

Clinical heterogeneity was assessed by considering the design of each trial. Where suspicion of clinical heterogeneity arose, the differences in study design among trials was considered.

Where possible and appropriate, the statistical heterogeneity was examined using the Chi^2 test. A P value below 0.10 indicated heterogeneity but was interpreted with caution. The I^2 statistic was calculated to assess the attribution of heterogeneity to the diversity of results from different trials.

Assessment of reporting biases

Due to the small number of trials included in the review, we did not investigate reporting bias through a funnel plot.

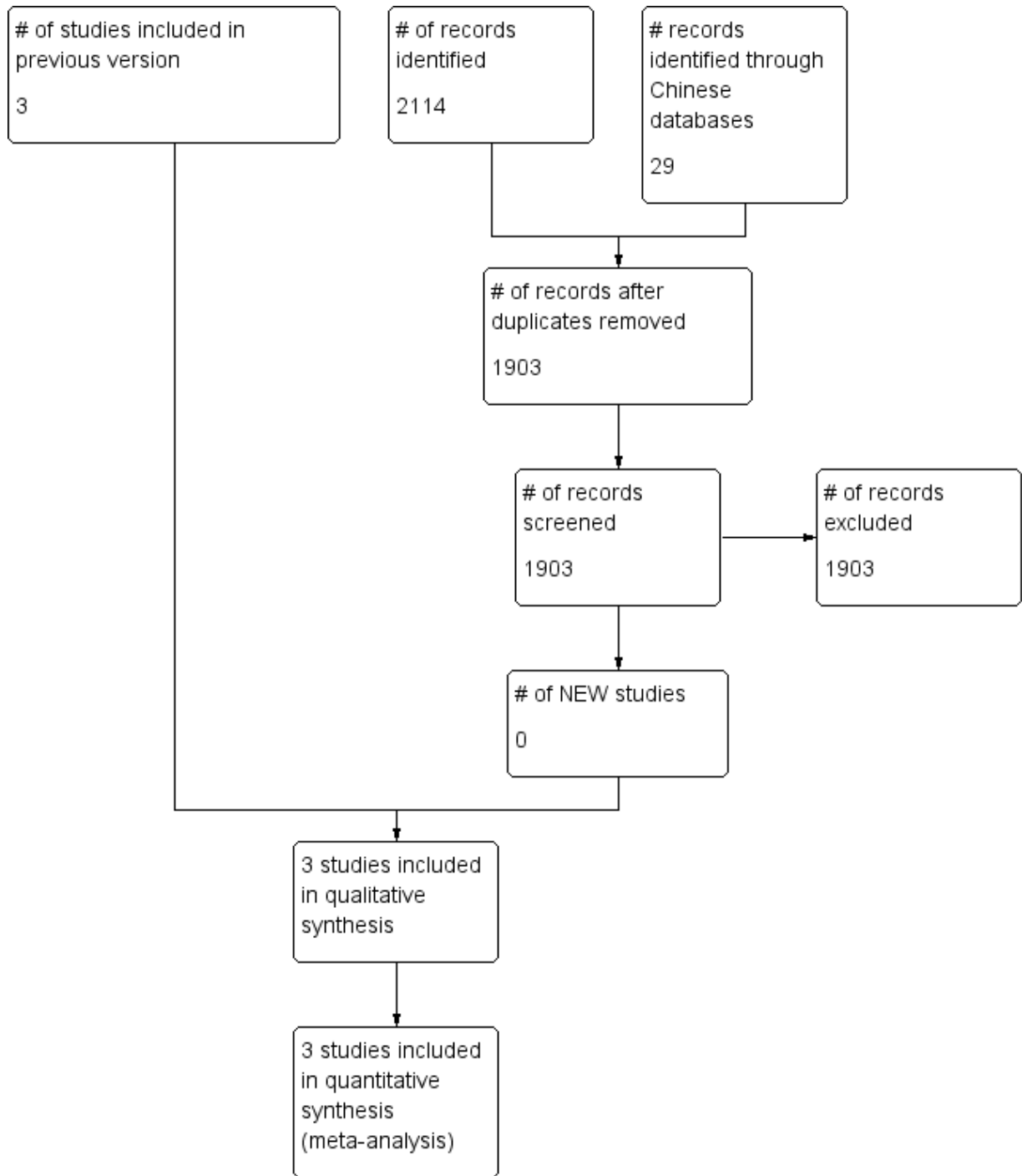
RESULTS

Description of studies

Results of the search

The study selection process is outlined in [Figure 3](#).

Figure 3. Study flow diagram for 2014 update.



The English language electronic search has retrieved a total of 2723 records across all years. Four RCTs (three completed and one ongoing) were identified in the first version of this review, and no new eligible studies have subsequently been found.

LL identified a total of 934 reports through a Chinese language search on Chinese language databases; none of them met the inclusion criteria.

LL identified one report while searching Google.com using the term 'clinical trial & paraquat', which was later excluded (Tsai 2009). No additional eligible RCTs were identified through screening reference lists or literature reviews.

Included studies

Three trials with a combined total of 164 participants are included in this review (Lin 1999; Lin 2006; Afzali 2008). All three compared the use of standard care alone versus standard care and glucocorticoid with cyclophosphamide for patients with paraquat poisoning. Mortality at final follow-up was the primary outcome in all three trials.

All three trials included moderate to severely paraquat poisoned patients who had a urine sodium dithionite test reaction of dark blue or navy blue. The Lin 2006 trial had an additional inclusion criteria of a predicted mortality of > 50% and ≤ 90% according to the Hart 1984 formula. (Readers of the review should therefore bear in mind that the trials included in the review had slightly different inclusion criteria and should interpret the findings of the review accordingly.) Patients with mild paraquat poisoning were not included in any trial.

Excluded studies

Two trials were excluded: in one trial the intervention was methylprednisolone only (Tsai 2009), and the other was a historical controlled trial (Perriens 1992).

Risk of bias in included studies

The trial by Lin 2006 had a relatively low risk of bias. The trial by Lin 1999 randomised all urine-positive patients but presented the outcomes for those who died within one week of poisoning separately from those who survived longer. Presenting the data separately is reasonable to a certain extent given the specific clinical features of paraquat poisoning, but also suggests reporting bias. The exact methods used for patient selection, randomisation and sequence concealment were not reported in the Afzali 2008 study but we were able to gain the necessary details through contact with the author and determined that the trial was at high risk of bias. Our judgements of the risk of bias are recorded in the 'Risk of bias' tables, and are displayed in [Figure 1](#) and [Figure 2](#).

Allocation

The Lin 2006 study used an appropriate method of sequence generation and allocation concealment. Lin 1999 generated the randomisation sequence using a random number table, but did not conceal the sequence. Afzali 2008 used alternation with no concealment, according to the author.

Blinding

None of the trials mentioned blinding of the treating physicians or patients. In Lin 1999 and Lin 2006 the statistician who contributed to the trial report was blinded to the allocation.

Incomplete outcome data

Mortality was the outcome of interest, and was reported in full in all trials.

Selective reporting

There was no selective reporting of mortality. The Lin 1999 study presented the mortality data by severity of poisoning and randomisation group, which appears to have been a post-hoc decision in the style of presenting results. However, we analysed the data according to intention to treat, which maintained the original randomisation.

Other potential sources of bias

No other potential source of bias was found.

Effects of interventions

All-cause mortality at the end of the follow-up period

All three trials reported death at the end of the follow-up period ([Analysis 1.1](#)). Patients who received glucocorticoid with cyclophosphamide in addition to standard care had a lower risk of death than those receiving standard care alone (RR 0.72; 95% CI 0.59 to 0.89). There was some statistical heterogeneity between trials ($\text{Chi}^2 = 5.96$, degrees of freedom (df) = 2 (P = 0.05); $I^2 = 66\%$).

Mortality at 30 days following the ingestion of paraquat

This outcome was not reported in any of the studies.

DISCUSSION

Summary of main results

This systematic review includes three trials (one of low methodological quality) with a combined total of 164 participants who had moderate to severe paraquat poisoning. Participants who received glucocorticoid with cyclophosphamide in addition to standard care had a lower risk of death than those receiving standard care alone.

Overall completeness and applicability of evidence

There are few RCTs involving paraquat poisoned patients. The review includes three small RCTs, one of which is of low quality. To enable further study of the effects of glucocorticoid and cyclophosphamide for paraquat poisoned patients, hospitals should provide this treatment as part of an RCT with allocation concealment. The findings of this review should be interpreted with caution until more data become available.

A large RCT in Sri Lanka has been terminated early due to the government's ban on the sale of paraquat. The results of this study will be included into the review in due course (if possible before the end of 2014). The study is described in the [Characteristics of ongoing studies](#) table.

Potential biases in the review process

This review was conducted according to predefined inclusion criteria and methodology to select and appraise eligible studies. The

search for trials was extensive, and was conducted on English and Chinese language databases. Publication bias is a consideration in any systematic review. Although there were only three small trials included in this review, we believe that due to the extent of the search for trials, these were the only RCTs addressing this research question at the time of the search.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the findings of three small RCTs of moderate to severely poisoned patients, glucocorticoid with cyclophosphamide in addition to standard care may be beneficial for patients with paraquat-induced lung fibrosis. The finding of this review should be interpreted with caution until more data become available.

Implications for research

To enable further study of the effects of glucocorticoid with cyclophosphamide for patients with moderate to severe paraquat poisoning, hospitals may provide this treatment as part of an RCT with allocation concealment.

ACKNOWLEDGEMENTS

We thank Karen Blackhall for providing the search strategy and the search of English language databases for previous versions of this review. We thank Xi Lv for searching Chinese language databases in 2012.

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Lin 1999 *{published data only}*

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Lin 2006 *{published data only}*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Afzali 2008

Methods	Randomised controlled trial
Participants	Patients with moderate to severe paraquat poisoning. Poisoning was determined by a navy blue or dark blue result of a urine sodium dithionite test
Interventions	All patients received: "...fixation of a nasogastric tube, gastric lavage with normal saline, charcoal-sorbitol gavage every two to four hours for three days, forced alkalinised diuresis in the first day of admission to the hospital, and haemodialysis of four hours duration for both groups." p.388 The intervention group also received: "...15 mg/kg of cyclophosphamide in dextrose saline (200 mL) was infused in two hours for two days. Methylprednisolone, one gram in 200 mL dextrose saline was also infused for four hours and was repeated for three consecutive days. Meanwhile, 15 mg/kg of mesna was prescribed (for four days) in order to avoid the side effects of cyclophosphamide." p.388
Outcomes	Mortality
Notes	Recruitment was from September 2003 to October 2005 Intervention group: 9 participants. 8 were male, 1 was female. Poisoning severity: 3 navy blue, 6 dark blue Control group: 11 participants. 8 were male, 3 were female. Poisoning severity: 4 navy blue, 7 dark blue

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	We contacted the author of the study, who told us alternation was used
Allocation concealment (selection bias)	High risk	The study author told us there was no allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not reported and, according to the author, was not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	The main outcome was death at final follow-up, and this was reported in full
Selective reporting (reporting bias)	Low risk	The study reported the main outcome, death at final follow-up, in full

Other bias	Low risk	We did not identify any other areas of bias
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Lin 1999

Methods	Randomised controlled trial
Participants	People who had ingested paraquat within the previous 24 hours, and had a urine sample that resulted in a navy blue or dark blue reaction to a sodium dithionite test
Interventions	All patients received: "To prevent absorption of paraquat from the gastrointestinal tract, active charcoal added in magnesium citrate was given through a nasogastric tube after gastric lavage with normal saline. All patients received two courses of 8-h active charcoal haemoperfusion therapy in the emergency room (ER), and dexamethasone 10 mg intravenous injection every 8 h was given for 14 d after admission." p.357 The intervention group also received: "In addition, the study group patients received pulse therapy after haemoperfusion at ER. Pulse therapy included 15 g/kg of CP in 5% glucose saline 200 ml and 1 g MP in the other 200 ml 5% glucose saline intravenously infused for 2 h/d. CP was infused for 2 d and MP for 3 d." p.357 (CP = cyclophosphamide; MP = methylprednisolone)
Outcomes	Mortality
Notes	Recruitment was from January 1992 to December 1997 Intervention group: 56 participants. 33 were male, 23 were female Control group: 65 participants. 45 were male, 20 were female

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...according to random digit methods." p.357
Allocation concealment (selection bias)	Unclear risk	There was no mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of the treating physician and patients was not reported "At the end of this study, to avoid bias, the data were collected and analysed by other doctors who were not aware of the study." p.357
Incomplete outcome data (attrition bias) All outcomes	Low risk	The main outcome was death at final follow-up, and this was reported in full
Selective reporting (reporting bias)	High risk	Information on the primary outcome, mortality is presented in full. However, the study report authors present the data according to severity of poisoning, although par-

Lin 1999 (Continued)

		participants were randomised into the study regardless of the severity of poisoning. We, the authors of this Cochrane review, have combined the results from the 2 tables on page 358 of their paper into the results of this review on an intention-to-treat basis to maintain the study investigators' original randomisation
Other bias	Low risk	We did not identify any other areas of bias. The presentation of results in the study report implies that the intervention is effective in moderately poisoned patients; but we have used an intention-to-treat analysis to summarise the findings in this review, which corrects this potential bias

Lin 2006

Methods	Randomised controlled trial
Participants	<p>Patients who: 1) arrived at the emergency department within 24 hours of ingesting paraquat, 2) were age 15 years or older, 3) had predicted mortality of > 50% and ≤ 90% according to the Hart 1984 formula, and 4) had urine sodium dithionite tests showing the colour dark blue or navy blue</p> <p>The exclusion criteria were: "Patients were excluded from the study if they had dermal exposure to paraquat; received intravascular injection of paraquat; did not have paraquat levels in biological fluids; arrived at the emergency room >24 hours after ingestion of paraquat; ingested paraquat due to major systemic diseases including cancer and heart, lung, renal, and liver diseases; or did not give informed consent." p.369</p>
Interventions	<p>All patients received: "To prevent absorption of paraquat from the gastrointestinal tract, activated charcoal 1 g/kg added to 250 mL of magnesium citrate was given through a nasogastric tube after gastric lavage with normal saline. In addition, all patients received two doses of 8-hr active charcoal-containing haemoperfusion therapy in the emergency room." p.369</p> <p>The control group received: "After haemoperfusion therapy, the control group received dexamethasone 5 mg in an intravenous injection every 6 hrs until their arterial blood gas showed PaO₂ 11.5 kPa (80mm Hg) or they died." p.369</p> <p>The intervention group received: "At the same time, the study group received pulse therapy with 15 mg/kg cyclophosphamide in 5% glucose saline 200 mL and 1 g of methylprednisolone in the other 200 mL of 5% glucose saline intravenously infused for 2 hrs per day. Cyclophosphamide was infused for 2 days and methylprednisolone for 3 day simultaneously. Preceding dexamethasone, a 5-mg intravenous injection every 6 hrs was given until the arterial blood gas showed PaO₂ 11.5 kPa (80 mm Hg). Repeated pulse therapy with 1 g of methylprednisolone in the other 200 mL of 5% glucose saline intravenously infused for 2 hrs per day for 3 days was given again if PaO₂ was 8.64 kPa (60 mm Hg). In addition, 15mg/kg/day cyclophosphamide was infused for 1 day again if patients' white cell counts were 3000/m³ and the duration was 2 wks after initial cyclophosphamide pulse therapy to avoid a severe leukopenia episode." p.369</p>
Outcomes	Mortality

Notes	<p>Participants were followed up for 6 weeks</p> <p>Recruitment was from January 1999 to December 2003</p> <p>Intervention group: 16 participants. 11 were male, 5 were female. Poisoning severity: 5 navy blue, 11 dark blue</p> <p>Control group: 7 participants. 5 were male, 2 were female. Poisoning severity: 1 navy blue, 6 dark blue</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"All study patients were randomly allocated to control and study groups in the proportion of 1:2 by means of a sequence of labelled cards contained in sealed numbered envelopes that were prepared by a statistical adviser." p. 369
Allocation concealment (selection bias)	Low risk	"...(the envelope was) opened by the researcher in the presence of patients." p.369
Blinding (performance bias and detection bias) All outcomes	High risk	"Neither stratification nor blinding was made in this study." p.369 "The data were collected and analysed by other doctors not familiar with the study." p.369
Incomplete outcome data (attrition bias) All outcomes	Low risk	The main outcome was death at final follow-up, and this was reported in full
Selective reporting (reporting bias)	Low risk	The study reported the main outcome, death at final follow-up, in full
Other bias	Low risk	We did not identify any other areas of bias. The inclusion criterion, using the Hart 1984 predictive mortality scale, was the main area for bias in this study (i.e. patients with a predicted mortality of $\geq 90\%$ or $< 50\%$ were excluded from the trial)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Perriens 1992	It was a historically controlled study, not randomised. "Patients admitted before October 10, 1986 received the standard treatment only, because i.v. cyclophosphamide and i.v. dexamethasone were not available in Suriname until that time. Patients presenting after October 10, 1986 received high-dose cyclophosphamide and dexamethasone treatment, in addition to standard treatment." p130

(Continued)

Tsai 2009	This study focused on methylprednisolone only
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Characteristics of ongoing studies [ordered by study ID]

ISRCTN85372848

Trial name or title	A randomised controlled trial of high-dose immunosuppression in paraquat poisoning (ISRCTN85372848)
Methods	Randomised controlled trial
Participants	Patients with paraquat poisoning Sample size: 600 (300 active, 300 placebo)
Interventions	Intervention: 2 days of cyclophosphamide 750 mg (if weight is < 50 kg) or 1 g (if weight is > 50 kg), and 3 days of methylprednisolone 1 g both by intravenous infusion over 1 hour. Steroids in the form of oral dexamethasone (8 mg 3 times daily) will be continued for the next 2 weeks. Patients will receive mesna 400 mg intravenous at start of therapy and 4 and 8 hours later to reduce risk of haemorrhagic cystitis Control: control patients will receive saline placebo infusion and placebo capsules
Outcomes	Primary: all-cause mortality in hospital Secondary: 1. All-cause mortality at 3 months' post-ingestion. 2. Lung function in survivors at 3 months
Starting date	30 August 2006
Contact information	Contact person: Pilane Liyanage Ariyananda South Asian Clinical Toxicology Research Collaboration (SACTRC) (Sri Lanka) SACTRC Department of Medicine University of Peradeniya 20000 Peradeniya Sri Lanka +94 (0)81 238 4556 ariyananda@sltnet.lk
Notes	Sponsors: 1. Syngenta Crop Protection AG (USA) 2. The Wellcome Trust (UK) (Grant reference number: 071669)

DATA AND ANALYSES

Comparison 1. All-cause mortality at final follow-up

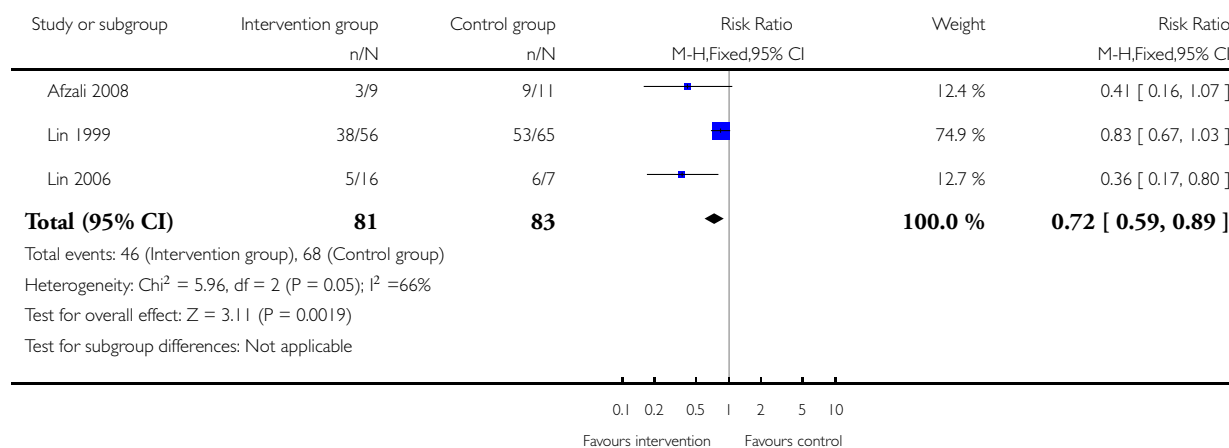
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at final follow-up	3	164	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.59, 0.89]

Analysis 1.1. Comparison 1 All-cause mortality at final follow-up, Outcome 1 All-cause mortality at final follow-up.

Review: Glucocorticoid with cyclophosphamide for paraquat-induced lung fibrosis

Comparison: 1 All-cause mortality at final follow-up

Outcome: 1 All-cause mortality at final follow-up



APPENDICES

Appendix I. Search Strategies 2014 update

For this recent update the search strategies were modified: the terms relating to *lung* were removed and the RCT filters were added. The strategies, as they were, did not retrieve the included studies even though they were indexed in MEDLINE and /or Embase. The included studies may have been retrieved either by screening reference lists. The added study filter is a modified version of the Ovid MEDLINE Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011); for Embase we added to the search strategy study design terms as used by the UK Cochrane Centre (Lefebvre 2011).

Other strategies for databases in the English language were not modified.

Cochrane Injuries Group's Specialised Register

#1 ((Paraquat or (methyl and viologen) or Dimethyl* or gramoxone or grammoxone or paragreen or Herbicide* or "Pyridinium compound" or pathclear or weedol)) AND ((cyclophosphamid* or carloxan or clafen or cycloblastin or cycloblastine or "cyclofos amide" or cyclofosamid or cyclofosfamide or cyclophosphan* or cycloxan or cyphos or cytophosphan* or cytozan or "endocyclo phosphate" or endoxan* or enduxan or "genoxalor mitoxan" or neosan or neosar or noristan or "nsc 26271" or "nsc 2671" or b-51)) [REFERENCE] [STANDARD]

MEDLINE (OvidSP)

1. exp Herbicides/
2. exp Paraquat/
3. (Paraquat or (methyl adj3 viologen) or Dimethyl* or gramoxone or grammoxone or paragreen or Herbicide* or Pyridinium compound* or pathclear or weedol).mp.
4. 1 or 2 or 3
5. exp Lung Diseases/
6. exp Pulmonary Fibrosis/
7. ((Pulmonary or lung) adj3 (fibrosis or fibroses)).ab,ti.
8. ((Alveolitis or alveolitides) adj3 fibrosing).ab,ti.
9. 5 or 6 or 7 or 8
10. exp Glucocorticoids/
11. glucocorticoid*.ab,ti.
12. exp Cyclophosphamide/
13. (cyclophosphamid* or carloxan or clafen or cycloblastin or cycloblastine or cyclofos amide or cyclofosamid or cyclofosfamide or cyclophosphan* or cycloxan or cyphos or cytophosphan* or cytozan or endocyclo phosphate or endoxan* or enduxan or genoxalor mitoxan or neosan or neosar or noristan or nsc 26271 or nsc 2671 or b-518 or procytox* or semdoxan or sendoxan).ab,ti.
14. 10 or 11 or 12 or 13
15. 4 and 9 and 14
16. (animals not (humans and animals)).sh.
17. 15 not 16

EMBASE (OvidSP)

1. exp Herbicide/
2. exp Paraquat/
3. exp pyridinium derivative/
4. (Paraquat or (methyl adj3 viologen) or Dimethyl* or gramoxone or grammoxone or paragreen or Herbicide* or Pyridinium compound* or pathclear or weedol).mp.
5. 1 or 2 or 3 or 4
6. exp Lung Disease/
7. exp lung fibrosis/
8. ((Pulmonary or lung) adj3 (fibrosis or fibroses)).ab,ti.
9. ((Alveolitis or alveolitides) adj3 fibrosing).ab,ti.
10. 6 or 7 or 8 or 9
11. exp Glucocorticoids/
12. glucocorticoid*.ab,ti.
13. exp Cyclophosphamide/
14. exp cyclophosphamide derivative/

15. (cyclophosphamid* or carloxan or clafen or cycloblastin or cycloblastine or cyclofos amide or cyclofosamid or cyclofosamide or cyclophosphan* or cycloxan or cyphos or cytophosphan* or cytohan or endocyclo phosphate or endoxan* or enduxan or genoxalor mitoxan or neosan or neosar or noristan or nsc 26271 or nsc 2671 or b-518 or procytox* or semdoxan or sendoxan).ab,ti.
16. 11 or 12 or 13 or 14 or 15
17. 5 and 10 and 16
18. exp animal/ not (exp human/ and exp animal/)
19. 17 not 18

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to January 2012 and ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) 1990 to January 2012

1. (Paraquat or Dimethyl* or gramoxone or grammoxone or paragreen or Herbicide* or pathclear or weedol or Pyridinium compound*) or (methyl same viologen)
2. (cyclophosphamid* or carloxan or clafen or cycloblastin or cycloblastine or cyclofos amide or cyclofosamid or cyclofosamide or cyclophosphan* or cycloxan or cyphos or cytophosphan* or cytohan or endocyclo phosphate or endoxan* or enduxan or genoxalor mitoxan or neosan or neosar or noristan or nsc 26271 or nsc 2671 or b-518 or procytox* or semdoxan or sendoxan)
3. ((Pulmonary or lung) SAME (fibrosis or fibroses)) OR ((Alveolitis or alveolitides) SAME fibrosing) OR (lung* SAME disease*)
4. 1 and 2 and 3

Clinical trials registries

Search terms: paraquat

Study results: All studies

Chinese databases

The databases originally searched in 2012 are now incorporated in a new Government sponsored database:

China National Knowledge Infrastructure (CNKI 数据库)

The authors also searched the following which were not included in the 2012 search:

WAN FANG DATA(万方数据库) (维普数据库)

The search string was limited to, Paraquat AND lung AND cyclophosphomide, due to the difficulties in using the search interfaces.

Appendix 2. Search methods for previous versions

Cochrane Injuries Group's Specialised Register

1. (Paraquat or (methyl and viologen) or Dimethyl* or gramoxone or grammoxone or paragreen or Herbicide* or "Pyridinium compound" or pathclear or weedol)
2. (cyclophosphamid* or carloxan or clafen or cycloblastin or cycloblastine or "cyclofos amide" or cyclofosamid or cyclofosamide or cyclophosphan* or cycloxan or cyphos or cytophosphan* or cytohan or "endocyclo phosphate" or endoxan* or enduxan or "genoxalor mitoxan" or neosan or neosar or noristan or "nsc 26271" or "nsc 2671" or b-51)
3. 1 and 2

CENTRAL (*The Cochrane Library*)

#1 MeSH descriptor Herbicides explode all trees

#2 MeSH descriptor Paraquat explode all trees

#3 (Paraquat or (methyl near3 viologen) or Dimethyl* or gramoxone or grammoxone or paragreen or Herbicide* or Pyridinium compound* or pathclear or weedol)

#4 (#1 OR #2 OR #3)

#5 MeSH descriptor Glucocorticoids explode all trees

#6 MeSH descriptor Cyclophosphamide explode all trees

#7 (cyclophosphamid* or carloxan or clafen or cycloblastin or cycloblastine or cyclofos amide or cyclofosamid or cyclofosamide or cyclophosphan* or cycloxan or cyphos or cytophosphan* or cytohan or endocyclo phosphate or endoxan* or enduxan or genoxalor mitoxan or neosan or neosar or noristan or nsc 26271 or nsc 2671 or b-518 or procytox* or semdoxan or sendoxan)

#8 (#5 OR #6 OR #7)

#9 (#4 AND #8)

Ovid MEDLINE(R)

1. exp Herbicides/
2. exp Paraquat/
3. (Paraquat or (methyl adj3 viologen) or gramoxone or paragreen or Herbicide* or Pyridinium Compound*).mp.
4. 1 or 2 or 3
5. exp Lung Diseases/
6. exp Pulmonary Fibrosis/
7. ((Pulmonary or lung) adj3 (fibrosis or fibroses)).ab,ti.
8. ((Alveolitis or alveolitides) adj3 fibrosing).ab,ti.
9. 5 or 6 or 7 or 8
10. exp Glucocorticoids/
11. glucocorticoid*.ab,ti.
12. exp Cyclophosphamide/
13. (Cyclophosphamide* or cytophosphan or cyclophosphane or procytox or sendoxan or b-518 or neosar or cytoxan or endoxan or nsc-26271).ti,ab.
14. 10 or 11 or 12 or 13
15. randomi?ed.ab,ti.
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. placebo.ab.
19. clinical trials as topic.sh.
20. randomly.ab.
21. trial.ti.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. (animals not (humans and animals)).sh.
24. 22 not 23
25. 4 and 9 and 14 and 24

CBM (1978 to April 2012), CMCC (1995 to April 2012), CMAc (1994 to April 2012)

1. exp herbicide/
2. exp paraquat/
3. 1 or 2
4. exp lung disease/
5. exp pulmonary fibrosis/
6. 4 or 5
7. exp corticosteroids/
8. steroids*.ab,ti.
9. exp cyclophosphamide/
10. 7 or 8 or 9 11.(randomised).ab,ti.
12. randomized controlled study.pt.
13. clinical controlled study.pt.
14. randomly.ab.
15. trial.ti.
16. 11 or 12 or 13 or 14 or 15.
17. 3 and 6 and 10 and 16.

WHAT'S NEW

Last assessed as up-to-date: 15 April 2014.

Date	Event	Description
25 May 2014	New search has been performed	The search has been updated to 15 April 2014. No new studies were identified. The results and conclusions remain the same The one ongoing study (ISRCTN85372848) was terminated early but some data are available. The study methodology and data have not been fully reported, but will be included into the review in due course
25 May 2014	New citation required but conclusions have not changed	Deirdre Beecher has been added as an author.

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 6, 2010

Date	Event	Description
25 May 2012	New search has been performed	The search has been updated to 1 February 2012. No new studies were identified. The results and conclusions remain the same
24 May 2012	New citation required but conclusions have not changed	The search has been updated, but no new studies were identified. The results and conclusions remain the same

CONTRIBUTIONS OF AUTHORS

For the 2010 and 2012 versions of this review: Luying Ryan Li (LL) and Chao You (CY) were responsible for writing the protocol. Bhuwan Chaudhary (BC) and LL selected the trials from English language databases. LL and YC selected trials from Chinese language databases. YC offered interpretation of the clinical features of paraquat poisoning and arbitrated on the inclusion of one trial ([Afzali 2008](#)). Emma Sydenham (ES), LL and BC independently assessed the risk of bias in the included trials and extracted data. LL and ES interpreted the data and wrote the manuscript. All authors agreed on the final manuscript.

For the 2014 version: Deirdre Beecher wrote the search strategy, searched English language databases, and screened the search results. Emma Sydenham screened some of the search results. Luying Ryan Li wrote the search strategy, searched Chinese language databases, and screened the search results. Chao You and Bhuwan Chaudhary also screened the Chinese language search results. DB, LL and ES updated the manuscript. All authors contributed to the updated review.

DECLARATIONS OF INTEREST

Luying Ryan Li: None known.

Emma Sydenham: None known.

Bhuwan Chaudhary: None known.

Deirdre Beecher: None known.

Chao You: None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol for this review, we said we would search the Chinese language databases Chinese bio-medical literature & retrieval system (CBM), Chinese medical current contents (CMCC), and Chinese medical academic conference (CMAC). These databases have now been included in the China National Knowledge Infrastructure database. For the 2014 update, we searched the databases China National Knowledge Infrastructure (数据库), WAN FANG DATA (万方数据库), and VIP (维普数据库).

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Cyclophosphamide [*therapeutic use]; Drug Therapy, Combination [methods]; Glucocorticoids [*therapeutic use]; Herbicides [*poisoning]; Immunosuppressive Agents [*therapeutic use]; Paraquat [*poisoning]; Poisoning [mortality]; Pulmonary Fibrosis [chemically induced; *drug therapy; immunology; mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans