Efecto del tratamiento combinado con esteroides y ciclofosfamida sobre la mortalidad en intoxicación por paraquat. Meta análisis

Efficacy of combined treatment with cyclophosphamide and glucocorticoids in paraquat poisoning mortality. A meta-analysis

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RESUMEN

Objetivo: realizar una revisión sistemática sobre la eficacia del uso combinado de ciclofosfamida más esteroides intravenosos contrastado con el hecho de no recibir esta combinación en adultos con intoxicación moderada a grave por paraquat, en disminuir la mortalidad a 30 días, en ensayos clínicos controlados al azar o cuasi al azar.
Metodología: búsqueda en bases de datos electrónicas, resúmenes de conferencias científicas, referencias de artículos relevantes y contacto con expertos de ensayos clínicos controlados con asignación al azar o cuasi azar de adultos intoxicados con paraquat, comparados con tratamiento convencional. Se utilizó doble entrada de datos con ReviewManager®5.
Resultados: hubo 3 ensayos clínicos (n=93) con aceptable calidad metodológica. La mortalidad del grupo de intervención fue 25% (12/47) vs. el grupo control 67% (31/46), RR 0,35 (IC95%: 0,21-0,61). La Q de Cochran (p= 0,93) y el I^2: 0% sugirieron homogeneidad. Se aplicó el modelo de efectos fijos y se hizo análisis de sensibilidad a través del uso del método de efectos aleatorios con resultados semejantes al de efectos fijos, lo que supone robustez del resultado. Los efectos adversos fueron leucopenia (37%), acné, alopecia e hiperglucemia. El pequeño número de estudios no permitió alcanzar suficiente poder para detectar sesgo de publicación.
Conclusiones: los resultados sugieren que la terapia inmunosupresora con ciclofosfamida y esteroides es eficaz para disminuir el riesgo de mortalidad en individuos con intoxicación moderada a severa por paraquat, razón por la cual debería recomendarse su uso.

Palabras clave: paraquat; ciclofosfamida; metilprednisolona; dexametasona; esteroides

ABSTRACT

Objective: systematic review to update evidence about whether the combined use of cyclophosphamide and intravenous glucocorticoids in adults with moderate to severe paraquat poisoning compared to conventional treatment, decreases the 30-day mortality rate in randomized and quasi-randomized controlled trials.
Methods: search in electronic databases, abstracts from scientific conferences, references in relevant articles and contact with experts. Randomized and quasi-randomized controlled trials on adult paraquat poisoning were included comparing this regimen with conventional treatment. Full text reviewed if they met inclusion criteria. Duplicate trials excluded. Two separate authors extracted data and double tool entrance data from ReviewManager® 5 was used.
Results: three randomized controlled trials identified (n=93) with acceptable methodology for meta-analysis. Intervention group mortality was 25% (12/47) vs. 67% (31/46) for control group and risk-ratio 0.35 (IC95%: 0.21-0.61). Cochran´s Q test

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p= 0.93 and I^2 0% suggesting homogeneity. According to this, a fixed effects model was used. Sensitivity analysis performed with random-effect yielding similar results to fixed effects model suggesting robust results. Therapy adverse events were leukopenia with no infections (37%), acne, hair loss and hyperglycemia. Small number of studies, so the power to detect publication bias was not reached.
Conclusions: results suggest immunosuppressive therapy is effective in decreasing mortality risk in adults with moderate to severe paraquat poisoning. Use of this therapy regimen is recommended.

Keywords: paraquat; cyclophosphamide; methylprednisolone; dexamethasone; glucocorticoids

BACKGROUND

Paraquat (PQ) is an herbicidal agent, whose oral ingestion produces high morbidity and mortality. Prognosis in suicidal ingestion depends on the swallowed concentrated product, ingested quantity and length of time before consultation. Global mortality has been reported to be between 54% in the United States to 71-80% in Asiatic countries[1,2]. In Colombia, there are no statistics on this medical condition but its high mortality is well known.

PQ promotes release of reactive oxygen species, which are responsible for the effects on cell membranes, enzymes and other structures[3-5]. It causes severe inflammation and consequently, gastrointestinal symptoms, hepatitis, acute renal failure and lung fibrosis.

According to doses and clinical manifestations, there are three stages in the classification of PQ poisoning severity: a) mild poisoning, b) moderate to severe poisoning and c) fulminant. *Mild poisoning* can cause gastrointestinal upset. Mortality rate is 0%; *moderate to severe poisoning* may result in gastrointestinal symptoms followed by multiple organ failure with acute renal failure and hepatitis at the end of the first week. Between the second and third weeks, alveolar and interstitial edema take place, leading to pulmonary fibrosis, acute respiratory distress, and death in about 30-60% of cases[6]. Fulminant poisoning has similar symptoms to moderate or severe poisoning, but its evolution is faster and death can occur in 24 to 48 hours in 100% of cases[6]. In a urine sample, this toxic is detected through the chemical reaction with sodium dithionite. This test is positive when blue color is produced. Light blue indicates mild poisoning and dark blue is for moderate to severe poisoning.

Treatment is focused in reduction of gastrointestinal absorption, increasing diuresis and immunosuppressive therapies to minimize or prevent lesions due to secondary reactive oxygen species release. There have been some efficacy trials evaluating therapies such as: hemoperfusion[7], hemodialysis, controlled hypoxia, superoxide dismutase, vitamins C and E, N-acetylcysteine, desferroxamine, clofibrate, gluthation, methallothioneine, xantin-oxidase inhibitors, selene, niacin, riboflavin, fatty acids, angiotensin, propanolol, putrescin, cadaverin, spermidin, chlorpromazine, anti-PQ anti-bodies[8], ambroxol, surfactant, nitrous oxide, steroids, radiotherapy[9], among others. Unfortunately, most recommended interventions have been based on low-level evidence trials and no certainty exists whether its use has improved survival. Some trials suggest cyclophosphamide treatment plus glucocorticoids could improve survival especially in severe poisoning[10-13], whereas there are other controversial trials about this subject[14,15]. Therapy effects with cyclophosphamide and glucocorticoids are supported on its immunosuppressive capacity limiting toxic and inflammatory response. Immunosuppressive treatment proposed for PQ poisoning has been used in patients with lung involvement in systemyc lupus erythematosus or Wegener´s granulomatosis, in which fewer adverse events have been shown[16].

Since thousands of patients around the world die every year as a consequence of PQ poisoning, and reported therapies have not yet shown consistent results, apart from having a high risk for complications, a systematic literature review proves necessary to assess the role of combined treatment with cyclophosphamide and glucocorticoids for these patients in order to establish its efficacy in mortality reduction and so, recommend its use.

The main objective of this study was to evaluate if combined treatment of cyclophosphamide plus intravenous glucocorticoids compared to no treatment with this regimen in adults with moderate to severe PQ poisoning decreases the 30-day mortality rate, in randomized or quasi-randomized controlled trials.

METHODS

Inclusion criteria

Both randomized or quasi-randomized controlled trials (those using an ID number, date of birth, input date and others as a method for treatment allocation) for PQ poisoning in adults were included, where combined use of cyclophosphamide and IV glucocorticoids was compared with conventional treatment to evaluate mortality. Conventional treatment is regarded as the use of any method of minimizing gastrointestinal absorption or the increase in elimination of the PQ that has already been absorbed or any antidote therapy.

Search strategy

The electronic databases MEDLINE, Cochrane Central Register of Controlled Trial -CENTRAL, EMBASE, LILACS and SCIELO were searched. This search included MeSH terms and free text as follows: Paraquat OR Paraquat poisoning) AND (Cyclophosphamide OR Methylprednisolone OR Dexamethasone OR Hydrocortisone OR Prednisone) AND (RCT OR Randomized Controlled Trial OR Quasi-Randomized Controlled Trial). There was no limitation for language, publication state or year of publication. The only limit used was age ("adults").

Furthermore, references from all selected articles and articles obtained by electronic search about PQ poisoning were reviewed in order to identify other relevant articles. We consulted abstracts from congresses of Toxicology from 1993 to 2009 from the American Academy of Clinical Toxicology (AACT) and European Association of Clinical Toxicologists (EAPCCT).

Studies selection

Two authors (LG and AL) separately reviewed the titles and abstracts of primary studies obtained from the electronic search. Articles meeting all inclusion criteria were completely reviewed. Any discordance was settled by consensus with a third author (AC). Reasons were reported for those articles not meeting inclusion criteria. Duplicate studies were excluded. Two authors (AC and RM) separately extracted data and ReviewManager® double entrance tool was used.

Moderate to severe PQ poisoning was defined as at least one dithionite sodium test with a dark blue result in a urine sample after 24 hours of PQ ingestion and no death in the first 48 hours. Mortality was defined by 30 days. Immunosuppressive treatment included any of two of following therapies: a) Cyclophosphamide 15 mg/kg/day for two days and dexamethasone 24 mg/day for fourteen days, or b) Cyclophosphamide 15 mg/kg/day for two days and methylprednisolone 1 g/day for two or three days.

The bias risk in the studies was assessed by two separate reviewers (LG and AL) according to sequence generation and allocation concealment, blinding, drop-outs and intention- to-treat analysis. Each item was classified as "YES" or "NO" if it was explicit and as "UNCLEAR" if it was not clearly expressed.

Drop-outs were classified as properly handled if more than 90% of participants allocated were analyzed and as unclear if they were not reported or improperly handled if less than 90% of participants allocated were analyzed.

Statistical Analysis

The relative risk (RR) and the 95% confidence interval (CI) were used for reporting cyclophosphamide plus glucocorticoids effects on PQ poisoning mortality in adults. Number needed to treat (NNT) with 95% CI, was calculated as the inverse of the absolute risk.

Results were transferred into a statistical graphic with forest plot for RR and its 95% CI. A Cochran's Q test with p value < 0.1 was significant for heterogeneity and I^2 less or equal to 25% was significant for homogeneity. All data were analyzed on Rev Man 5 Software (Review Manager version 5.0 Copenhagen, Denmark: Nordic Cochrane Centre, Cochrane Collaboration; 2008).

Publication bias was assessed by funnel plot. Potential heterogeneity sources were pre-specified such as sex and short (metylprednisone 1g/day for 2 or 3 days) and long courses (dexamethasone 24 mg/day for 14 days) of glucocorticoids. These subgroup analyses were planned a priori. Sensitivity analyses were pre-specified by treatment assignment (randomized and quasi-randomized allocation) and for the biggest and smallest magnitude of effect.

RESULTS

Selection of studies

The search strategy yielded 34 trials. Of these, 3 were excluded because of duplicity in different databases (Figure 1). Common reasons for excluding other articles (28 in total) were different methodological designs or different interventions (Appendix 1). Finally, 3 randomized clinical trials for qualitative and quantitative analysis were included. All of them, evaluated efficacy for combined cyclophosphamide and glucocorticoids treatment for moderate to severe PQ poisoning (Table 1).

Control Group

Control group, included trials using conventional treatment such as gastric lavage, activated charcoal (unique or repeated doses), cathartics and increasing elimination by forcing diuresis, hemodialysis or hemoperfusion. In two trials, dexamethasone was used[11,12].

Intervention Group

All included patients, received the same treatment as the control group and additionally received cyclophosphamide 15 mg/Kg/day for 2 days and methylprednisolone 1g/day for 3 days. One of the included studies[12], considered the therapy mentioned above plus dexamethasone (5mg IV every 6 hours) until Pa02 ≥80 mmHg; if Pa02 <60 mmHg methylprednisolone was repeated for 3 days and Cyclophosphamide for 1 day if leucocytes were > 3 000 two weeks after the first dosis (Table 1). Another study[13] used Mesna to decrease the adverse event risk associated to cyclophosphamide use.

Outcomes

One published article[12] evaluated the 6 week mortality rate in moderate to severe paraquat poisoning; others[11,13] evaluated it during 2-3 weeks.

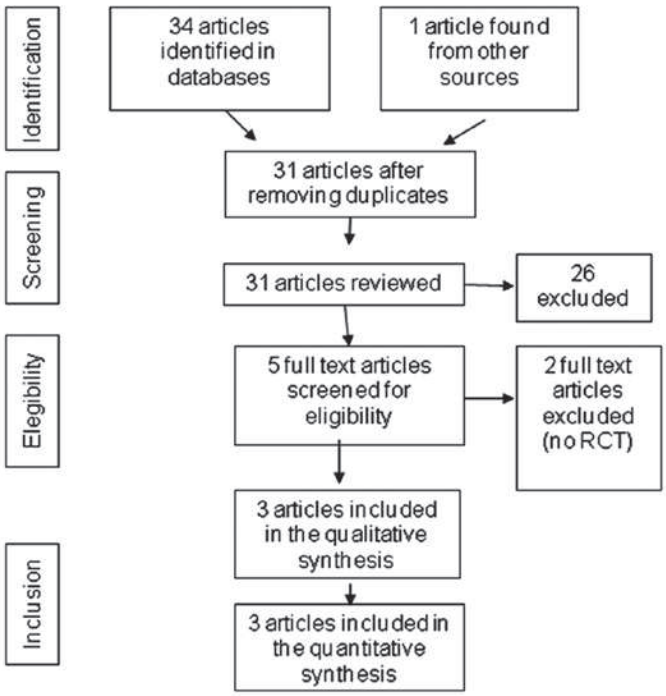


Figure 1. Selection of studies

Table 1. Characteristics of Included Studies

Source	Population	n	Conventional Treatment (control)	Interventions	Outcome
Lin JL *et al.*,1999[11]	Patients with moderate to severe paraquat poisoning (measured by strongly positive urine dithionite test and mortality after a week)	50	Gastric Lavage Activated charcoal Magnesium Citrate Hemoperfusión Dexamethasone 10 mg every 8 hours for 14 days.	Conventional treatment CP: 15mg/kg/día for 2 days + MP 1 g/day for 3 days.	Mortality at 2 weeks from first week after poisoning until research was finished
Lin JL *et al.*, 2006[12]	Patients with moderate to severe paraquat poisoning (defined for risk of die between 50-90% measured by serum concentrations, according to Hart *et al.*[9]).	23	Gastric Lavage Activated charcoal Magnesium Citrate Hemoperfusion Dexamethasone 5 mg intravenous injection every 6 hours until Pa02 ≥80mmHg or patient´s death.	Conventional treatment CP (15mg/kg/day for 2 days) + MP (1 g/ day for 3 days). After DX (5mg IV every 6 hours) until Pa02 ≥80mmHg. MP was repeated for 3 days If Pa02<60mmHg. CP for 1 day if leucocytes >3000 and more than 2 weeks for first dose.	Mortality at least 6 weeks
Afzali S *et al.*, 2008[13]	Patients with moderate to severe paraquat poisoning((measured on the urine samples by sodium dithionite reaction test strong positive and clinical manifestations)	20	Gastric Lavage Repeated Charcoal-sorbitol doses Forced alkalinized diuresis Hemodialysis	Conventional treatment CP (15 mg/kg/día por dos días) + MP (1 g/día por 3 días) + mesna 15mg/kg por 4 días.	Mortality during research

CP: Cyclophosphamide MP: Methylprednisolone DX: Dexamethasone

Risk of bias in Included Studies

The methodological quality is shown in Table 2. Although authors from three included trials mentioned randomized allocation, one clearly explained how the sequence generations were obtained and only one described allocation concealment. Only one trial specified there was no blinding and it was judged that the outcome measurement is not likely to be influenced by lack

Table 2. Risk of bias in included studies

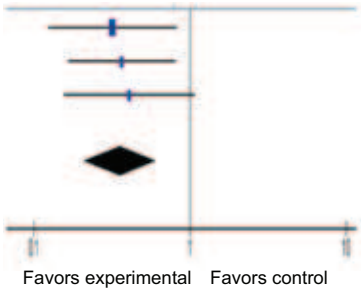
Author	Year	Sequence Generation	Allocation Concealment	Blinding	Drop-outs	Intention-to-treat analysis
Lin JL	1999	Unclear	Unclear	Unclear (there was blinding outcome assessors)	Yes (properly handled)	Yes
Lin JL	2006	Unclear	Yes (envelopes)	No	Yes (properly handled)	Yes
Afzali S	2008	Unclear	Unclear	Unclear	Yes (properly handled)	Yes

of blinding. Blinding outcome could modify co-interventions but in this case it was not a critical factor due to high PQ poisoning mortality and reduced efficacy for conventional therapies. All trials had a proper follow up. In spite of the fact that intention-to-treat analysis was not specified, all patients were analyzed in the group in which they were assigned. In general, risk for bias in included studies was related to sequence generation.

Intervention Effects

A total of 93 participants with moderate to severe PQ poisoning were included from three studies. Mortality for intervention group was 25% (12/47) and 67% (31/46) for control group with a RR= 0.35 (95% CI: 0.21-0.61; p= 0.93; I^2=0%). Cochran's Q test and I^2 suggested homogeneity since fixed effects model was used (Figure 2). NNT was calculated with 95% CI (3; 95% CI: 2- 4).

Study or Subgroup	Experimental Group	Control Group	Weight %	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Lin JL 1999	4/22	16/28	46.1	0.32 (0.12-0.82)	
Lin JL 2006	5/16	6/7	27.3	0.36 (0.17-0.8)	
Afzali 2008	3/9	9/11	26.5	0.41 (0.16-1.07)	
Total events	12/47	31/46	100%	0.35 (0.21-0.61)	



Heterogeneity X^2=0.14 gl=2 p=0.93; I^2=0%
Test for overall effect: Z=3.76 (p=0.0002)

Figure 2. Mortality in Randomized Clinical Trials

Subgroup analyses were not necessary since homogeneity was found. Sensitivity analysis for type of sequence generation was pre-specified; however, quasi-randomized trials were not found. The biggest positive and negative magnitude effect studies were excluded, being their combined RR for the former 0.39 (0.21-0.72) and 0.34 (0.17-0.64) for the latter, suggesting robust results. Magnitude effects and confidence intervals obtained from the fixed effects model were similar to the results from the random effects model.

Some adverse events were reported from the authors. Lin JL *et al.* (1999), found leukopenia in 36.4% (8/22) of patients that received cyclophosphamide. Hair loss and acne were also reported. Lin JL *et al.* (2006), described leukopenia in 6 patients which appearedr after 2 weeks, 5 patients developed fever without infection condition, hyperglycemia was present in 1 patient and hair loss and acne were present in 11 participants. Afzali S *et al.* (2008) did not inform the presence or absence of adverse events.

Publication bias

No evidence of publication bias was found by funnel plot and we think it might due to exhaustive database and manual search (Figure 3)

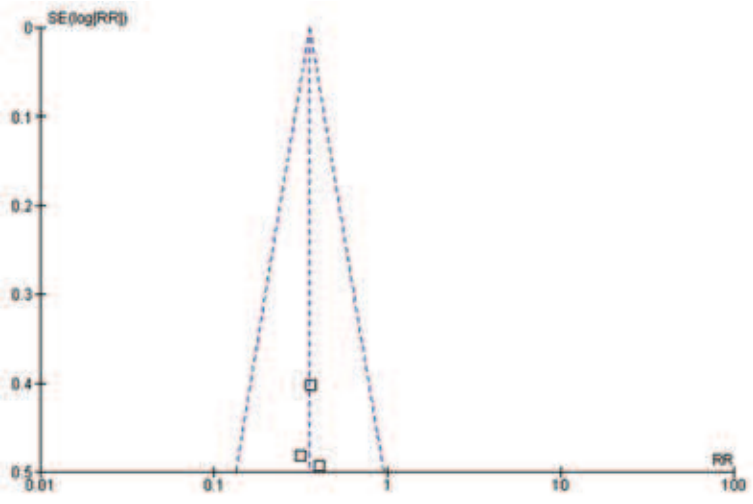


Figure 3. Funnel plot

DISCUSSION

This current meta-anaylisis evaluated cyclophosphamide and glucocorticoids therapy efficacy in adults with moderate to severe PQ poisoning. Randomized and quasi-randomized controlled trials were included comparing cyclophosphamide plus glucocorticoids to conventional treatment. Included studies were homogeneous and a beneficial effect was found with intervention, considering that mortality was reduced between 39-70% compared to control group (RR: 0.35, 95% CI: 0.21-0.61). These results were confirmed by sensitivity analysis.

It is not yet known, how this therapy could be useful; however, it is known that severe inflammation is part of the pathophysiology of lung fibrosis resulting from PQ poisoning and a cyclophosphamide anti-inflammatory effect is presumed to be beneficial. Likewise, glucocorticoids have also been shown to suppress superoxide production by neutrophils and macrophages and the formation of superoxide through the arachidonic acid cascade[17]. This action is further powered by cyclophosphamide therapy. Life-threatening adverse effects never occurred. Therefore, the benefit is greater than the risk with this intervention.

A meta-analysis is a statistical strategy for assembling the results of several studies into a single precise estimate and that is what was obtained here. Search strategy without restriction for language, year or publication state, reduce the risk of losing important trials; nevertheless, a publication bias could not be demonstrated and one of the limitations was the small number of studies found. Maybe this does not allow us to reach enough power to detect any bias if it really exists. Another limitation was methodological studies quality, mainly or the absence of description of sequence generation found in all included studies. Lin JL *et al.*

(1999) and Afzali S *et al.* (2008), did not describe how allocation concealment and blinding was performed.

In conclusion, combined therapy with cyclophosphamide and glucocorticoids could decrease mortality related to moderate to severe PQ poisoning in adults. Hence, the authors recommend this therapy for this kind of patients.

DECLARATION OF CONFLICT OF INTEREST

None of the authors have conflict of interest.

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9 Talbot AR, Barner MR. Radiotherapy for the treatment of pulmonary complications of paraquat poisoning. Human Toxicol. 1988;7:325-32.

10 Addo E, Poon-King T. Leucocyte supression in treatment of 72 patients with paraquat poisoning. Lancet. 1986; 1: 1117-1120.

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13 Afzali S, Gholyaf M. The effectiveness of combined treatment with methylprednisolone and cyclophosphamide in oral paraquat poisoning. Arch Iran Med. 2008;11(4):387-391.

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Appendix 1. Characteristics of excluded studies

Article	Reasons for exclusion
1. Descatha A, Mégarbane B, Garcia V, Baud F. Delayed immunosuppressive treatment in life-threatening paraquat ingestion: a case report. J Med Toxicol. 2009 Jun;5(2):76-9. PubMed PMID: 19415592.	Case report
2: Barrueto F, Lee C, Pajoumand M, Yeung SY, Starr PE. Use of sirolimus in a case of severe paraquat poisoning. Clin Toxicol (Phila). 2008 Sep;46(8):778-9. PubMed PMID: 19238741.	Other immunosuppressive
3: Choi Y, Cho K, Yoon S, Lee H, Choi Y. A case of paraquat intoxication caused by intravenous injection. Am J Emerg Med. 2008 Sep;26(7):836.e3-4. PubMed PMID: 18774055.	Case report
4: Agarwal R, Srinivas R, Aggarwal AN, Gupta D. Experience with paraquat poisoning in a respiratory intensive care unit in North India. Singapore Med J. 2006 Dec;47(12):1033-7. PubMed PMID: 17139398.	Case report
5: Jenq CC, Wu CD, Lin JL. Mother and fetus both survive from severe paraquat intoxication. Clin Toxicol (Phila). 2005;43(4):291-5. PubMed PMID: 16035207.	Case report
6: Lin NC, Lin JL, Lin-Tan DT, Yu CC. Combined initial cyclophosphamide with repeated methylprednisolone pulse therapy for severe paraquat poisoning from dermal exposure. J Toxicol Clin Toxicol. 2003;41(6):877-81. PubMed PMID: 14677801	Case report
7: Hsu HH, Chang CT, Lin JL. Intravenous paraquat poisoning-induced multiple organ failure and fatality--a report of two cases. J Toxicol Clin Toxicol. 2003;41(1):87-90. PubMed PMID: 12645975.	Cases report
8: Chen GH, Lin JL, Huang YK. Combined methylprednisolone and dexamethasone therapy for paraquat poisoning. Crit Care Med. 2002 Nov;30(11):2584-7. PubMed PMID: 12441774.	Case report
9: Botella de Maglia J, Belenguer Tarín JE. [Paraquat poisoning. A study of 29 cases and evaluation of the effectiveness of the “Caribbean scheme”]. Med Clin (Barc). 2000 Oct 28;115(14):530-3. Spanish. PubMed PMID: 11141378.	Cases series
10: Lin JL, Wei MC, Liu YC. Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. Thorax. 1996 Jul;51(7):661-3. PubMed PMID: 8882069; PubMed Central PMCID: PMC472485.	Not clinical trial
11: Perriëns JH, Benimadho S, Kiauw IL, Wisse J, Chee H. High-dose cyclophosphamide and dexamethasone in paraquat poisoning: a prospective study. Hum Exp Toxicol. 1992 Mar;11(2):129-34. PubMed PMID: 1349219.	Not randomization or quasi-randomization
12: Nogué S, Munné P, Campañá E, Bertrán A, Reig R, Rodamilans M. [Failure of a cyclophosphamide dexamethasone combination in paraquat poisoning]. Med Clin (Barc). 1989 Jun 10;93(2):61-3. Review. Spanish. PubMed PMID: 2666783.	Case report

13: Hamaguchi T, Goto K, Fujiwara M, Okada H, Arakawa S, *et al.* [4 cases of paraquat poisoning]. Hinyokika Kiyo. 1989 Feb;35(2):367-9. Review. Japanese. PubMed PMID: 2660506.	Cases report
14: Savy FP, Duval G, Her B, Canu P, Fintelz P. [Failure of chemotherapy and radiotherapy in pulmonary fibrosis caused by paraquat]. Ann Fr Anesth Reanim. 1988; 7(2):159-61. French. PubMed PMID: 3364814.	Other type of intervention
15: Addo E, Poon-King T. Leucocyte suppression in treatment of 72 patients with paraquat poisoning. Lancet. 1986 May 17;1(8490):1117-20. PubMed PMID: 2871379.	Case report
16: Bársony J, Kertész F. Investigation of adrenal steroids and 25-hydroxy-cholecalcipherol in human gramoxone poisoning. Arch Toxicol Suppl. 1985; 8:280-3. PubMed PMID: 2937388.	Other type of intervention
17: Addo E, Ramdial S, Poon-King T. High dosage cyclophosphamide and dexamethasone treatment of paraquat poisoning with 75% survival. West Indian Med J. 1984 Dec; 33(4):220-6. PubMed PMID: 6523848.	Not RCT
18: Webb DB, Williams MV, Davies BH, James KW. Resolution after radiotherapy of severe pulmonary damage due to paraquat poisoning. Br Med J (Clin Res Ed). 1984 Apr 28;288(6426):1259-60. PubMed PMID: 6424818; PubMed Central PMCID: PMC1441111.	Other type of intervention
19: Harrison LC, Dortimer AC, Murphy KJ. Fatalities due to the weed-killer paraquat. Med J Aust. 1972 Sep 30; 2(14):774-7. PubMed PMID: 4644636.	Case report
20: Oreopoulos DG, Soyannwo MA, Sinniah R, Fenton SS, Bruce JH, McGeown MG. Acute renal failure in case of Paraquat poisoning. Br Med J. 1968 Mar 23; 1(5594):749-50. PubMed PMID: 5641444; PubMed Central PMCID: PMC1985491.	Case report
21: Eisenman A, Armali Z, Raikhlin-Eisenkraft B, Bentur L, Bentur Y, Guralnik L, *et al*. Nitric oxide inhalation for paraquat-induced lung injury. J Toxicol Clin Toxicol. 1998;36(6):575-84.	Other type of intervention
22: Johnston CC, Stremler R, Horton L, Friedman A. Effect of repeated doses of sucrose during heel stick procedure in preterm neonates. Biol Neonate. 1999 Mar;75(3):160-6	Other type of intervention
23: García J, Frontado C, Tilac C, Rendón C, Brewster F, González A, *et al*. Intoxicación moderada a severa por paraquat: tratada con esteroides e inmunosupresores: datos preliminares / Med Interna (Caracas); 2000; 16(3):177-181.	Cases report
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