

Effect of pulse therapy with glucocorticoid and cyclophosphamide in lung fibrosis due to paraquat poisoning in rats

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ABSTRACT

الأهداف: تقييم مدى فعالية العلاج المكثف بالسيكلوفوسفاميد (cyclophosphamide) وميثيل بريدنيسولون (methylprednisolone) في الحماية من التليف الرئوي الناتج عن التسمم بالباراكوات.

الطريقة: أُجريت هذه الدراسة التجريبية في مستشفى سينا، تبريز، إيران وذلك خلال الفترة من فبراير إلى أغسطس 2009م. لقد تم تخفيف التسمم الحاد في الجرذان بواسطة حقن مبيد البُرااكوات داخل الصفاق (15 ملغ/كلغم). لقد تم تقسيم المجموعات المعالجة (10 جرذان في كل مجموعة) إلى مجموعتين وهما: المجموعة التي عولجت علاجاً مكثفاً بكل من السيكلوفوسفاميد (15 ملغ/كلغم) وميثيل بريدنيسولون (26.5 ملغ/كلغم) داخل الصفاق ولمدة 3 أيام (PQ+P)، والمجموعة التي عولجت علاجاً تقليدياً بمضادات الأكسدة مثل: فيتامين أ، وه، والريباف المضاد للأكسدة (PQ+Vit) (N-acetylcysteine)، هذا بالإضافة إلى مجموعة التحكم (PQ)، وتم تقييم فعالية أنواع العلاج في الحماية من التليف الرئوي في اليوم الخامس عشر من بداية التجربة. لقد تم الحصول على درجة التليف الرئوي من خلال معايير أشكروفت، وفيما بعد تم إجراء التقدير شبه الكمي من أجل تحليل النتائج وعمل مقارنة بين المجموعات التي تضمنتها الدراسة.

النتائج: أشارت النتائج إلى أن معدل درجة التليف الرئوي في المجموعة (PQ) كان 4.60 ± 1.20 ، وفي المجموعة (PQ+P) 2.93 ± 0.72 ، وكان في المجموعة (PQ+Vit) 4.25 ± 1.08 . لقد كانت درجة التليف الرئوي في المجموعة (PQ+P) أقل كثيراً من المجموعة (PQ) ($p=0.011$)، فيما لم يكن هناك اختلافاً واضحاً في معدل التليف الرئوي بين المجموعتين (PQ) و (PQ+Vit).

خاتمة: أثبتت الدراسة مدى فعالية العلاج المكثف بالسيكلوفوسفاميد وميثيل بريدنيسولون في الحماية من التليف الرئوي، ولذلك فنحن ننصح بإتباع مثل هذا العلاج مع طرق العلاج التقليدية أثناء معالجة التسمم بالباراكوات.

Objectives: To evaluate the effectiveness of cyclophosphamide and methylprednisolone pulse therapy in the prevention of pulmonary fibrosis due to paraquat poisoning in rats.

Methods: This study was carried out in Sina Hospital, Tabriz, Iran, between February and August 2009. Acute poisoning in rats was induced by intraperitoneal injection of Paraquat (15 mg/kg). We planned 2 separate treatment groups (10 rats each), pulse therapy with methylprednisolone (26.5 mg/kg) and cyclophosphamide (15 mg/kg) intraperitoneally for 3 days (PQ+P) and treatment with conventional anti-oxidant drugs including vitamin A, vitamin E, and N-acetylcysteine (PQ+Vit). Prevention of pulmonary fibrosis was evaluated on the fifteenth day. A semi-quantitative determination of lung fibrosis was carried out (Ashcroft staging criteria) on the lung sections and results compared with the paraquat control group (PQ).

Results: The mean score of fibrosis in the PQ was 4.60 ± 1.20 , in PQ+P was 2.93 ± 0.72 , and for PQ+Vit groups was 4.25 ± 1.08 . The score of fibrosis in the PQ+P was significantly lower than the PQ group ($p=0.011$), while there was no significant difference in the average score of lung fibrosis between the PQ and PQ+Vit groups.

Conclusion: Pulse therapy with cyclophosphamide and methylprednisolone significantly prevented pulmonary fibrosis. Therefore, we recommend it along with conventional therapies in the treatment of acute paraquat poisoning.

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Paraquat is one of the most potent herbicides all around the world. It is the third most widely used poison in most countries. Thousands of deaths due to accidental or suicidal usage of this agent are reported.¹ In developing countries, paraquat is used despite its potent danger and many incidences of accidental exposure via skin are recorded, and may kill a person.^{1,2} Paraquat is a very toxic and dangerous agent and may contaminate via the gastrointestinal tract, skin, or even by inhalation. There is no effective therapy in paraquat poisoning, so investigators focused on anti neutrophilic therapies.³ According to the World Health Organization classification, paraquat is in class II with moderate lethal effects. In amounts less than 17 mg/kg, paraquat may kill a person (less than one teaspoonful).¹ There is no effective antidote for it. This agent may damage the lungs, heart, kidney, liver, and other organs. The patient may die due to multi organ failure. Paraquat alters lipid metabolism and after peroxidation produces free radicals harmful to cell membranes, nucleic acids, and proteins. Paraquat is a potent superoxide anion producer, agents hazardous to body organs.⁴ It must be emphasized that the main target organ in paraquat poisoning is the lungs. It may induce pulmonary edema, lung membrane damage, and finally pulmonary fibrosis.⁵ According to previous reports, there are limited double blind controlled studies on the effectiveness of corticosteroids in this poisoning; on the other hand, control groups are not identical and they are not randomly selected. Therefore, this study was planned to evaluate immunosuppressant therapy with glucocorticoids and cyclophosphamide. The lethal dose in rats according to LD 50 (gives the amount of the substance required, usually per body weight, to kill 50% of the test population) is 283 mg/kg in females, and 344 mg/kg in male rats orally. However, by intraperitoneal injection, 18 mg/kg and 19 mg/kg are fatal.⁶ To date drug absorption reduction in the gastrointestinal tract was the corner stone of treatment. It is suggested that hemoperfusion may increase survival of patients.⁷ Unfortunately, other therapeutic attempts such as controlled hypoxia, vitamin C, vitamin E, N-acetylcysteine (NAC), deferoxamine, and nitric oxide has not had any useful effects.⁸ For the first time in 1971, immunosuppressant therapy for paraquat poisoning was reported by Malone et al,⁹ but up to now its efficacy has not been clarified in most of the reported studies, and in these studies there were no control groups.¹⁰ We found only one randomized clinical trial, which according to the author had many methodological problems, and was an elementary form of study.¹¹ Li et al¹² introduced glucocorticoid with cyclophosphamide for the prevention of paraquat induced lung fibrosis. Huang et al¹³ described the role of connective tissue growth factors and α -smooth muscle actin in pulmonary

fibrosis among acute paraquat poisoned rats. In our study, we performed an animal parallel randomized clinical trial under standard conditions to detect the efficacy of pulse therapy with methylprednisolone and cyclophosphamide in paraquat induced pulmonary fibrosis.

Methods. This experimental study was carried out in the Tuberculosis and Lung Research Center, Tabriz, Iran, between February and August 2009. Fifty Wistar rats (weight 200-250 gr and 7-8 weeks old) were enrolled in this study; we kept the rats for one week for adaptation. Standard food and drinkable water were available. The Animal Ethical Committee of Tabriz University of Medical Sciences approved all steps of our research. After one week, the rats were divided into 5 equal groups (each one has 10 rats). On the first day, 15 mg/kg of paraquat solution diluted in normal saline (N/S) (20%) was injected intraperitoneally in groups I, II, and III. One hour after injection, NAC, 100 mg/kg vitamin E, and 10 mg/kg vitamin C were injected intraperitoneally in group III (Table 1). One hour after paraquat injection in group II, and immediately in group IV pulse therapy with methylprednisolone (26.5 mg/kg) and cyclophosphamide (15 mg/kg) was initiated intraperitoneally (paraquat induced fatal gastrointestinal damage, and rats died due to this problem in a pilot study; however, we had planned this study to clarify the effects of paraquat on the lung, so it was injected intraperitoneally) on days 0, one, and 2 (Table 1). The rats were kept under observation for 15 days in their cages. After death, both lungs were dissected and stored in 10% formalin solution, also the time of death was recorded. At the end of the fifteenth day, the rats were anesthetized with ether and their lungs dissected and stored in 10% formalin solution for further histopathological studies. After processing, lung samples were stained (hematoxylin & eosin method) and studied by light microscopy for fibrosis. Grading of lung fibrosis is reported by the Ashcroft criteria¹⁴ (Table

Table 1 - Drugs administered in the studied groups.

| Group | Drugs used |
|-------------|--|
| I: PQ | Paraquat 15 mg/kg |
| II: PQ+P | Paraquat 15 mg/kg; Methylprednisolone 26.5 mg/kg; Cyclophosphamide 15 mg/kg |
| III: PQ+Vit | Paraquat 15 mg/kg; Vitamin C 10 mg/kg; Vitamin E 100 mg/kg; N-acetylcysteine 100 mg/kg |
| IV: CP+MP | Methylprednisolone 26.5 mg/kg; Cyclophosphamide 15 mg/kg |
| V: N/S | Normal saline |

2). All samples were randomly numbered and studied by 2 pathologists. The average of scores obtained was reported as a semi-qualitative indicator of pulmonary fibrosis in each rat.

Using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), the findings were analyzed by the Mann-Whitney U test, nonparametric statistical method. The efficacy of pulse therapy and antioxidants was evaluated by chi-square test. In this study $p < 0.05$ was considered significant. All data are reported as mean \pm SD.

Results. Fifty rats in 5 equal groups enrolled in this study. The weight of the rats was 228.00 ± 14.02 grams. The weight difference between the groups was not significant ($p = 0.741$). After 15 days, mortality in the paraquat (PQ) group was 50% (5 rats), in the paraquat pulse therapy (PQ+P) group, it was 20% (2 rats), in the pulse therapy control group (CP+MP) it was 10% (one rat), in the N/S group we had no mortality, and in the paraquat plus antioxidant (PQ+Vit) therapy it was 40% (4 rats) (Figure 1). The life expectancy of rats after 15 days in the PQ group was 10.60 ± 5.31 , in the PQ+P group this was 13.50 ± 3.37 , and in PQ+Vit group this was 11.90 ± 4.93 days. In the CP+MP group it was 14.80 ± 0.68 , and in the N/S control it was 15.00 ± 0 days. Some rats died due to the effects of the paraquat and they were autopsied to detect the effects of paraquat on the lungs.

Histopathological pulmonary findings in the dead rats were lung congestion, interstitial edema, infiltration of inflammatory cells, macrophages, pulmonary hemorrhage, and pulmonary fibrosis. The mean fibrosis score in the PQ group was 4.60 ± 1.20 (range: 3.50-6.50), and in PQ+P was 2.93 ± 0.72 (range: 2.00-4.50). Non-parametric analysis revealed that the mean difference of fibrosis scores between the PQ and PQ+P groups was significant, and the fibrosis score in the PQ+P group was significantly lower than the PQ group ($p = 0.011$). The mean fibrosis score in the PQ+Vit group was 4.25 ± 1.08 (range: 3.00-6.00), and it was lower than the PQ group,

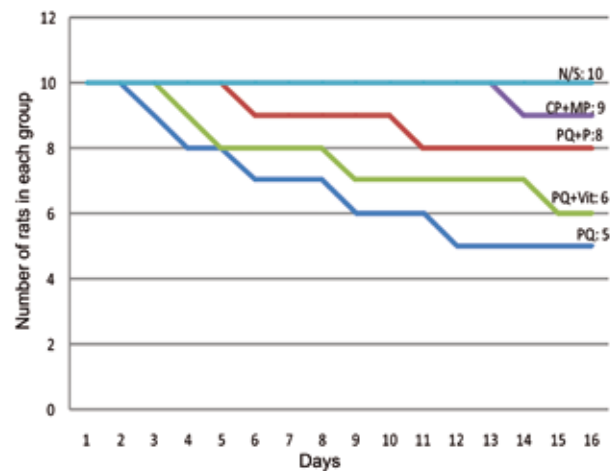


Figure 1 - Fifteen day survival of rats.

however, this difference was not statistically significant ($p = 0.404$). The mean fibrosis score in the control pulse therapy group (CP+MP) (without paraquat) was 0.39 ± 0.48 , and it was statistically different from the PQ group ($p = 0.001$). The mean fibrosis score in the N/S group was 0.50 ± 0.52 , and its difference compared with the PQ group was significant ($p = 0.001$). However, nonparametric analysis revealed no difference between the control pulse therapy and N/S group ($p = 0.66$). The mean fibrosis score in the PQ+P was significantly lower than the PQ+Vit group ($p = 0.014$). Finally, evaluation of the fibrosis score in the 5 groups using Kruskal-Wallis nonparametric method was carried out, and revealed that all studied groups had significant differences in pulmonary fibrosis score ($p = 0.001$).

Discussion. Paraquat has unique properties and is used as a herbicide all around the world. After ingestion of this agent (accidentally or for suicide attempt), it accumulates in all the body organs, especially the lungs. In severe poisonings, the human or animal subject will die.^{15,16} Unfortunately, all the suggested therapeutic methods are reported as case studies or in small groups, and we do not have any strict documentation on their efficacy. In some studies, the effects of antioxidant therapy, chelating agents, and recently, captopril were reported.^{17,18} Agarwal et al¹⁸ reported 5 patients from India treated with methylprednisolone and cyclophosphamide pulse therapy and then dexamethasone daily; 2 out of 5 survived. After clarifying its effect in pulmonary edema and fibrosis formation, some immunosuppressive and antioxidant methods such as methylprednisolone and cyclophosphamide were suggested.¹⁹ Our study was also designed according to these reports. In this experimental double blind randomized study, we compared the efficacy of methylprednisolone and cyclophosphamide

Table 2 - Criteria for lung fibrosis grading.¹⁴

| Grade of fibrosis | Histological features |
|-------------------|--|
| 0 | Normal lung |
| 1 | Minimal fibrous thickening of alveolar or bronchial walls |
| 2/3 | Moderate thickening of walls without obvious damage to lung architecture |
| 4/5 | Increased fibrosis with definite damage to lung structure and formation of fibrous bands or small fibrous masses |
| 6/7 | Severe distortion of structure and large fibrous area (honeycomb lung) |
| 8 | Total fibrous obliteration of the field |

pulse therapy with conventional antioxidant therapy in paraquat induced pulmonary fibrosis.

We used semi quantitative histopathology parameters, and the result showed that the pulmonary fibrosis score in the PQ+P group was significantly lower than PQ and PQ+Vit groups. Although the fibrosis score was lower in the PQ+Vit group, it was not statistically significant ($p=0.08$). In this study, the mortality rate after 15 days was 20% in the PQ+P group, 50% in the PQ group, and 40% in the PQ+Vit group, so the efficacy of pulse therapy was remarkable. Jian et al,²⁰ in a human study reported that survival in pulse therapy with prednisolone, cyclophosphamide, and etanercept were better than usual therapies. In our study, the survival rate after 15 days was 80% in the pulse therapy group, and 60% in the antioxidant group, which was similar to Jian's report. In another study, Afzali and Gholyaf²¹ showed that in 45 patients with moderate to severe paraquat poisoning, the mortality rate with the usual therapy was 81.8%, and 33.3% with the usual therapy plus cyclophosphamide, methylprednisolone and mesna ($p<0.05$). In our study, the mortality rate in the pulse therapy was 20%, and in the usual therapy group was 50%, so this method of therapy was more effective, also Afzali and Gholyaf used mesna in their method, and for this reason these 2 results are not completely comparable.²²

As mentioned previously, these reports were not associated with a randomized control group and patient samples were not enough, and due to ethical problems, effect of variables such as dose, kind of paraquat poisoning, general condition, underlying problems, and latency period were not adequately controlled. Combined therapy was usually used, so estimation of each one is impossible, and because of these biases selection of them is not evidence based.

Rocco et al²³ showed the effects of glucocorticoids in pulmonary tissue remodeling in the first phase of acute pulmonary injury. In this study 2 mg/kg of methylprednisolone was injected in paraquat poisoned rats, and this kind of therapy blocked the collagenesis and elastogenesis in rats. In their study, methylprednisolone in mild lung injuries improved pulmonary functions. In more severe cases, it altered tissue impedance and reduced extracellular matrix. The useful effects of steroids were maintained over 30 days. In our study, the pulse therapy was also effective in pulmonary function improvement and fibrosis prevention, but a limited amount of collagen was detected in the immunohistochemical studies. Some reports revealed that sodium salicylate may prevent paraquat induced apoptosis in the rat lung, and hydrocortisone may have additive effects, so anti inflammatory therapy with glucocorticoids was suggested.^{22,24}

Chen et al²⁵ studied the effects of methylprednisolone in oxygenation of pulmonary tissues in acute lung injury during paraquat poisoning in rats. Methylprednisolone (30mg/kg) was injected intraperitoneally. This kind of therapy improved tissue oxygenation after 3 intraperitoneal injections, and an increasing methylprednisolone dose reduced inflammatory cell counts in lavage fluid. In another study,²⁶ the pulmonary response of intratracheal surfactant and dexamethasone was evaluated. It revealed gas transport improvement and reduction of inflammation and pulmonary damage in paraquat poisoning. However, surfactant alone associated with low dose dexamethasone had limited effects.

Lavango et al²⁷ studied betamethasone effects in pulmonary paraquat damage in rats. It was seen that one mg/ml betamethasone before paraquat injection introduced inflammatory cells migration and malondialdehyde formation, so survival may be decreased. They concluded that the paraquat combined with betamethasone had worsened mortality. These results are contrary to our reports, however, the type of corticosteroid and route of administration was different, so additional studies are necessary.

Yeh et al²⁸ showed that NAC inhibited malondialdehyde serum levels and superoxide anions in poisoned rats. The NAC was effective in lung injury and inflammatory cells infiltration, but the improvement of survival was not significant. In our study also NAC, vitamin E, and vitamin C had no significant effect on pulmonary fibrosis, edema, honeycombing, and fibrosis. Dubaybo et al²⁹ also suggested early administration of glucocorticoids in paraquat poisoning.

In conclusion, we showed that pulse therapy with cyclophosphamide and methylprednisolone in moderate and severe paraquat poisoning significantly decreased pulmonary complications, and the efficacy of this type of therapy in pulmonary fibrosis is remarkable. Based on our knowledge of the high mortality of paraquat poisoning, and in the absence of any antidote, this type of therapy is highly recommended for this type of poisoning. We had some limitations in that it was a semi-quantitative study and the fibrosis scoring was according to the observer. Therefore, quantitative immunohistochemical studies may be more accurate. We suggest similar studies are designed at different time points of exposure, as this may be more helpful for future therapy.

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