The Effectiveness of Combined Treatment with Methylprednisolone and Cyclophosphamide in Oral Paraquat Poisoning

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Background: Paraquat is a bipyridil herbicide and in appropriate and careful usage, will not be health threatening. Most adult cases of intoxication are due to suicidal attempts rather than accidental exposure. Therapeutic response has been reported to be appropriate with high doses of cyclophosphamide and glucocorticoids and survival is reported to be approximately 75%. So, this study was designed to evaluate the effects of combined treatment with cyclophosphamide and glucocorticoids in patients with paraquat poisoning.

Methods: During a two-year period 45 patients with paraquat poisoning were admitted to Sina Hospital, Hamadan, Iran, of whom 20 had moderate to severe intoxication. Eleven patients (group 1) received conventional treatment and nine patients (group 2) received conventional treatment plus intravenous infusions of cyclophosphamide 15 mg/kg daily for two days, methylprednisolone one gram daily for three days, and mesna 15 mg/kg for four days.

Results: The mean age±SD in group 1 was 25±10 years and in group 2 was 26±10 years. In group 1 three patients were females and eight patients were males. In group 2 one patient was female and eight patients were males. There were no differences between the groups in the time elapsed from ingestion to presentation at hospital or in the beginning of hemodialysis. The mortality rate in group 1 was 81.8% and in group 2 was 33.3% (P<0.05). All fatalities caused by acute respiratory distress syndrome.

Conclusion: Pulse therapy with cyclophosphamide and methylprednisolone may be effective in preventing respiratory failure and reducing mortality in patients with moderate to severe paraquat poisoning.

Keywords: Cyclophosphamide • methylprednisolone • paraquat • survival

Introduction

Paraquat (PQ) is a bipyridil herbicide. In appropriate and careful usage, it will not be health threatening. Most adult cases of intoxication are due to suicidal attempts rather than homicidal or accidental exposure.1-4 PQ is available in commercial 20% concentrate form, as 2.5% granules, and as 0.2% aerosol.1

The exact mechanism of toxicity is not known completely, however, PQ releases free oxygen radicals (superoxide and hydrogen peroxide) near the mucus membranes resulting in mucosal damages in different organs.1,2

Symptoms of PQ ingestion are dose dependent. Its intoxication is categorized to mild, moderate, and severe on the basis of the doses used. Doses less than 20 mg/kg result in mild intoxication, which presents with transient vomiting, diarrhea, and oropharyngeal burns. It mostly resolves without further sequelae. Patients who ingest 20 – 50 mg/kg PQ present with severe oropharyngeal burns, pharyngeal pseudomembranes, vomiting, severe diarrhea, abdominal pain, and acute renal and hepatic insufficiency. Initial symptoms are followed by progressive pulmonary fibrosis and death within two to ten weeks. Ingestions of more than 50 mg/kg PQ (approximately one mouthful of toxin), will cause death within 72 hours because of
The effectiveness of combined therapy with MP and CP in oral PQ poisoning

multiple organ failure. Autopsy findings have shown pallor and fatty changes in the liver, and renal cortical pallor. In patients who lived longer, pulmonary changes including stiff edema, completely hard hyaline membrane, patchy bleeding (spotting) in alveoli, and fibrotic changes have been reported.

Analysis of urine for PQ is an appropriate method for diagnosis and determining the severity of poisoning. Previous studies have shown that urine PQ concentration in the first 24 hours after poisoning is a good indicator to determine the severity of poisoning. Urine PQ test may be a qualitative or semiqualitative evaluation and it can simply be done at emergency room. However, common treatments such as dialysis, alkalinized diuresis, and using charcoal have been disappointing. Although therapeutic response has been reported with high doses of cyclophosphamide (CP) and glucocorticoids and survival is mentioned to be approximately 75%, other studies disagree this result. So, this study was designed to evaluate the effects of combined treatment with CP and methylprednisolone (MP) in patients with PQ poisoning.

Materials and Methods

This randomized controlled trial was performed on 20 patients with moderate to severe PQ poisoning referred to the Emergency Department of Sina Hospital, Hamadan, Iran, from September 2003 through October 2005.

Sodium dithionite reaction test was done on the urine samples of all patients as soon as possible. The positive results of the test are on the basis of PQ reduction by sodium dithionate in alkaloid environment, which results in the production of blue radicals. Navy blue (NB) or dark blue (DB) colors usually indicate significant PQ poisoning.

The studied patients were divided into three groups on the basis of the results of the sodium dithionite reaction test and the clinical manifestations: 1) Fulminant poisoning: The urine test was NB color. All of these patients died during the first few days (three to four days) after poisoning because of multiorgan involvement, such as acute tubular necrosis, myocarditis, hepatic necrosis, and pulmonary bleeding. 2) Moderate to severe poisoning: The urine test color was NB or DB and the clinical manifestations were oropharyngeal burns, pharyngeal pseudomembranes, vomiting, severe diarrhea, and acute renal and hepatic failure.

3) Mild poisoning: The urine test was colorless or light blue and the clinical manifestations included transient diarrhea, vomiting, and buccal hyperemia, which mostly resolved without further sequelae.

Of the 45 patients assessed in this study, 15 patients with mild and 10 patients with fulminant poisoning were excluded. So, 20 patients remained. Of them 11 patients received “conventional treatment” (group 1) and nine patients received “conventional” treatment plus “new treatment” (group 2) randomly.

Conventional treatment included fixation of a nasogastric tube, gastric lavage with normal saline, charcoal-sorbitol gavage every two to four hours for three days, forced alkalinized diuresis in the first day of admission to the hospital, and hemodialysis of four hours duration for both groups.

In addition, 15 mg/kg of CP in dextrose saline (200 mL) was infused in two hours for two days in group 2. MP, one gram in 200 mL dextrose saline was also infused for four hours and was repeated for three consecutive days for this group as well. Meanwhile, 15 mg/kg of mesna was prescribed (for four days) in order to avoid the side effects of CP.

Basic daily laboratory tests included liver function tests (LFT), complete blood count (CBC), arterial blood gas (ABG), blood urea nitrogen (BUN), and creatinine. Chest radiography was repeated every 48 hours. Creatinine >1.4 mg/dL, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) more than 70 IU/L, and PaO2<70 mmHg (in the room air) were considered as acute renal failure (ARF), hepatitis, and hypoxia, respectively. Finally, autopsy was done for all expired patients.

The patients and the relatives were informed about the probable side effects of therapeutic methods. Analysis was performed using SPSS software version 13 by t-test and Fisher’s exact test.

In addition, this survey was approved by the Ethics Committee of Hamadan University of Medical Sciences.

Results

In this randomized controlled trial, 20 patients with moderate to severe PQ poisoning were studied. All the patients abused PQ in order to commit suicide.
Clinical findings and laboratory data of both groups at the first day of admission are presented in Table 1.

Analysis of the results demonstrated no significant difference between the two groups on the first day of admission. Biochemical findings in both groups during the admission period are shown in Table 2.

The mortality rate was higher in group 1 (81.8%) compared with group 2 (33.3%; \( P < 0.05 \)).

Autopsy findings included perioral lesions, oral and pharyngeal burns, esophageal and gastric patchy erosions and patchy bleeding, pallor of the liver and fatty changes (in the microscopic evaluation), and renal cortical pallor in patients with ARF. Pulmonary pathologic changes included stiff edema, lung stiffness, alveolar exudates, hyaline membrane formation, alveolar patchy hemorrhages, and fibrous changes in the patients who survived longer.

Table 1. Clinical findings and laboratory data of both groups at the first day.

<table>
<thead>
<tr>
<th></th>
<th>(Group 1)</th>
<th>(Group 2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=11)</td>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>25±10</td>
<td>27±10</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8(72.7%)</td>
<td>8(88.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>3(27.3%)</td>
<td>1(11.1%)</td>
<td></td>
</tr>
<tr>
<td>Time from poisoning to hospital admission (hr)</td>
<td>4.5±2</td>
<td>5±2</td>
<td>NS</td>
</tr>
<tr>
<td>Time from poisoning to hemodialysis for the first time (hr)</td>
<td>10±2</td>
<td>10±2</td>
<td>NS</td>
</tr>
<tr>
<td>Poisoning severity (on the basis of urine test)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navy blue</td>
<td>4(36.4%)</td>
<td>3(33.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dark blue</td>
<td>7(63.6%)</td>
<td>6(66.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.9±1.2</td>
<td>2.1±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Serum ALT (IU/L)</td>
<td>50±30</td>
<td>55±30</td>
<td>NS</td>
</tr>
<tr>
<td>Total serum bilirubin (mg/dL)</td>
<td>2±1.3</td>
<td>2±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial PaO2 at room air (mmHg)</td>
<td>82±10</td>
<td>83±10</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>18.1%</td>
<td>33.3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS=not significant; ALT=alanine aminotransferase.

Table 2. Biochemical findings in both groups during the admission period.

<table>
<thead>
<tr>
<th></th>
<th>(Group 1)</th>
<th>(Group 2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=11)</td>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>6.35±4.7</td>
<td>2.5±1.5</td>
<td>( P &lt; 0.05 )</td>
</tr>
<tr>
<td>ARF</td>
<td>100%</td>
<td>66.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Serum ALT (IU/L)</td>
<td>400±200</td>
<td>150±50</td>
<td>( P &lt; 0.05 )</td>
</tr>
<tr>
<td>Total serum bilirubin (mg/dL)</td>
<td>10±3</td>
<td>4.7±3</td>
<td>( P &lt; 0.05 )</td>
</tr>
<tr>
<td>Arterial PaO2 at room air (mmHg)</td>
<td>60±25</td>
<td>70±15</td>
<td>NS</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>72.7%</td>
<td>44.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>100%</td>
<td>100%</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS=not significant, ARF=acute renal failure, ALT=alanine aminotransferase.

Discussion

Our results showed that the mortality rate was significantly lower in group 2 (\( P < 0.05 \)). Nonetheless, the mortality rate is still high in patients with PQ poisoning.\(^{18}\)

Previous studies have shown that treatment with CP and MP could reduce the mortality rate in these patients.\(^{14,19-21}\) Our results similarly suggest that pulse therapy with CP and MP may improve the survival rate in patients with moderate to severe PQ poisoning.

Comparing with previous studies,\(^{11-13}\) our study clarifies the efficacy of pulse therapy in treating patients with moderate to severe PQ poisoning. In addition, the pulse therapy may also have improved the survival rate of our patients, although the exact mechanism of PQ toxicity is still unknown.

It seems that, acute respiratory distress syndrome (ARDS) in PQ-intoxicated patients is the...
The effectiveness of combined therapy with MP and CP in oral PQ poisoning

major cause of death. Therefore, survival may increase by controlling the pulmonary tissue inflammation.22

Pulse therapy with MP is known as a strong anti-inflammatory treatment in clinical practice. CP exerts a wide range of immunomodulatory effects that influence virtually all components of the cellular and humoral immune response and reduces the severity of inflammation. In addition, CP-induced leukopenia may contribute to reduce pulmonary inflammatory changes in patients with PQ poisoning.23,24

In a previous study,25 which was confirmed by a subsequent study,18 it was found that the respiratory function and arterial blood oxygen concentrations of PQ-poisoned survivors after treatment with CP and MP could gradually improve to nearly normal.

Multiple organ dysfunction is another main etiology of death in these patients. Related studies have shown that plasma endothelin level increases in patients with multiple organ dysfunction syndrome.26,27 So, it may be one of the diagnostic clinical indices for evaluating the stage of organ damage. Hence, the severe inflammation of multiple organs such as kidney and liver may play the predominant role in the lethal outcome in such patients.

The present study shows that CP and MP may prevent further renal and hepatic damages during the admission.

The efficacy of pulse therapy may be due to the reduction of the severity of hypoxia. Although CP may induce pulmonary toxicity in clinical practice, the frequency is only 1% or less,18 and most reports are from patients with malignant diseases who received multiple agents.28

In the present study, ARDS was determined to be the main etiologic factor for death in autopsy and no death occurred because of the side effects of CP or MP pulse therapy.

Homicide, according to the results of other studies, is rare with this poison.34 In our study, all patients used PQ in order to commit suicide and there were no cases of homicide or accidental use.

In most of the studies, poisoning was more frequent in male patients.29 In our study, there were no significant differences between the two treatment groups with respect to age and sex, though most of the patients were males.

We did not check plasma PQ level in our patients, which can be the limitation of this study.

However, the plasma PQ level falls very quickly after poisoning. Because previous studies10 showed that plasma and urine tests within the first 24 hours of intoxication were good predictors of outcome and prognosis, the urine dithionite test is a reasonable indicator of the severity of PQ poisoning in our patients. In addition, urine test can be performed easily and quickly in any situation and no specific equipment is needed.

According to the results of this test, all of our patients showed evidence of moderate to severe poisoning.

In our study and the other studies,17,29 clinical and laboratory findings (developing ARF, increased ALT, hyperbilirubinemia, and hypoxia) at arrival to emergency room were similar in the two groups but they differed during the next days of admission.

Another limitation of the present study is the small number of patients, thus it requires to be confirmed in larger randomized controlled trials.

There were no severe complications in the new treatment group, and this suggests that pulse therapy is safe and well-tolerated and, therefore, may improve survival.

References

11. Hampson EC, Pond SM. Failure of hemoperfusion and hemodialysis to prevent death in paraquat poisoning. A


