Paraoquat (PQ) is a widely used bipyridyl contact herbicide with a good safety record when used properly. Most cases of PQ poisoning result from PQ suicidal ingestion. There are three degrees of severity in PQ poisoning (1, 2). Mild poisoning can cause oral irritation and gastric upset, and brings complete recovery. Moderate to severe poisoning produces acute renal failure, and in severe cases, hepatitis followed by pulmonary fibrosis, leading to death after 2 to 3 wk. A cute fulminant poisoning results in death within 1 wk from multiple organ failure and cardiovascular collapse. Retrospective studies (3–6) show that good predictors of outcome may be plasma and urine concentrations within the first 24 h of intoxication. The urine PQ tests taken on admission are reasonable guides to predict the severity of poisoning and have the advantage that a qualitative or semiquantitative result may be easily and rapidly obtained in an emergency situation (5–7).

The results of treatments for PQ poisoning, including absorbents, pharmacological approaches (8), radiotherapy (9), hemodialysis, and hemoperfusion (10), were disappointing. Although the high-dose cyclophosphamide (CP) and dexamethasone (DX) treatments, including intravenous CP 5 mg/kg/d and DX 24 mg/d for 14 d, had a 75% survival rate after PQ poisoning (11), a subsequent study (12) did not demonstrate the efficacy of this approach. Therefore, the efficiency of high-dose CP and DX in PQ poisoning remains controversial. Recently, pulse therapy with CP and methylprednisolone (MP), including intravenous CP or MP 1 g/d for 2 to 3 d, has been used to treat effectively many patients with severe lung damage from systemic lupus erythematosus (SLE) and Wegener’s granulomatosis (13, 14), with greater efficacy and less side effects than those of high doses of CP therapy. In addition, our preliminary report (15) demonstrated that pulse therapy might be effective in treating patients with moderate to severe PQ poisoning. Because the previous study was not prospective and only included a small number of patients, we designed the prospective study to evaluate its efficacy in treating a large group of PQ-poisoned patients.

METHODS

This study was approved by the clinical research committee of Chang Gung Memorial Hospital and had the informed consent of all patients. This prospective study lasted from January 1992 to December 1997. During this period, 142 patients with PQ poisoning were admitted to our hospital within 24 h after ingestion. In urine samples taken on arrival at our emergency department, PQ was immediately detected by the sodium dithionite reaction. The sodium dithionite test is based on the reduction of PQ by sodium thionite under alkaline condition to form its stable blue radical ion. A strong “navy blue” (NB) or “dark blue” (DB) generally indicates significant PQ ingestion and subsequent poor prognosis (5–7). Patients were classified as having: (1) fulminant poisoning if their urinary dithionite reaction yielded a NB or DB and if they died from multiple organ failure within 1 wk after intoxication; (2) moderate to severe poisoning if the urine PQ tests were NB or DB or if they died from hypoxia and lung fibrosis more than 6 d after intoxication; (3) mild poisoning if the urine PQ tests were colorless or light blue (1–3). Most plasma PQ concentrations were not checked owing to the limitations of our facilities. Patients with strongly positive urine dithionite tests (NB or DB color) randomly received conventional or pulse therapy for PQ intoxication according to random digit methods. At the end of this study, to avoid bias, the data were collected and analyzed by other doctors who were not aware of the study. A total of 50 patients with moderate to severe PQ poisoning were included in this study. Seventy-one patients with fulminant poisoning and 21 patients with mild poisoning were excluded.

To prevent absorption of PQ 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 hemoperfusion therapy in the emergency room (ER), and dexamethasone 10 mg intravenous injection every 8 h was given for 14 d after admission. In addition, the study group patients received pulse therapy after hemoperfusion 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. Blood gas analysis, blood cells count, serum creatinine, chest X-ray, and liver function tests were regularly checked.

Definition (12)

A cute renal failure was diagnosed if the serum creatinine increased to 1.4 mg/dl (i.e., mean normal value + 2 standard deviations). Hepatitis was diagnosed when aspartate aminotransferase (ST) and alanine aminotransferase (ALT) values were > 70 U/L (normal value is < 35 U/L) or when total bilirubin was > 3.0 mg/dl (normal value is < 1.4 mg/dl). Hypoxia was diagnosed if a patient had an arterial blood gas analysis of PaO2 < 70 mm Hg at room air.

Data Analysis

The differences between groups were compared with Student’s t tests. To clarify the effects of the pulse therapy on the clinical course of the
There were no significant differences in age, sex, time elapsed from ingestion to arrival at ER, the beginning of hemoperfusion, and severity of PQ poisoning between the study group and control group. The prevalence rates of acute renal failure, hepatitis, and hypoxia at the third day after PQ ingestion were not significantly different between the two groups (Table 2). The clinical course and biochemical data of both groups of patients are presented in Table 3. The peak serum creatinine and total bilirubin concentrations of the study group were significantly lower than in the control group (serum creatinine: 2.5 ± 1.8 mg/dl versus 5.3 ± 4.1 mg/dl, p = 0.0040; total bilirubin: 2.6 ± 4.8 mg/dl versus 7.2 ± 8.6 mg/dl, p = 0.046). Otherwise, the lowest PaO₂ of the study group was marginally significantly higher than that of the control group (67.9 ± 27.3 mm Hg versus 52.2 ± 29.4 mm Hg, p = 0.0584).

The mortality rate of the study group (4 of 22, 18.2%) was higher than that of the control group (6 of 37, 16.2%). A p value less than 0.05 was considered significant. All data were presented as mean ± SD.

### RESULTS

Seventy-one patients with fulminant PQ poisoning who died within 1 wk after intoxication were excluded (Table 1). Fifty patients were enrolled in the study. Most were young adults. A l l were suicidal and had ingested liquid PQ concentrate (24%). Twenty-two patients received pulse and conventional therapies in the study group and 28 received conventional therapy only in the control group. Age, sex, and clinical conditions were equally represented in both groups (Table 2). There were no significant differences in age, sex, time elapsed from ingestion to arrival at ER, the beginning of hemoperfusion, and severity of PQ poisoning between the study group and control group. The prevalence rates of acute renal failure, hepatitis, and hypoxia at the third day after PQ ingestion were not significantly different between the two groups (Table 2). The clinical course and biochemical data of both groups of patients are presented in Table 3. The peak serum creatinine and total bilirubin concentrations of the study group were significantly lower than in the control group (serum creatinine: 2.5 ± 1.8 mg/dl versus 5.3 ± 4.1 mg/dl, p = 0.0040; total bilirubin: 2.6 ± 4.8 mg/dl versus 7.2 ± 8.6 mg/dl, p = 0.046). Otherwise, the lowest PaO₂ of the study group was marginally significantly higher than that of the control group (67.9 ± 27.3 mm Hg versus 52.2 ± 29.4 mm Hg, p = 0.0584).

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### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 37)</th>
<th>Study Group (n = 34)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>38.2 ± 16.3</td>
<td>35.7 ± 13.6</td>
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<tr>
<td>Sex</td>
<td>27 M, 10 F</td>
<td>20 M, 14 F</td>
<td>0.2226</td>
</tr>
<tr>
<td>Time elapsed from ingestion to arrival at ER, h</td>
<td>5.4 ± 5.3</td>
<td>5.3 ± 2.6</td>
<td>0.8426</td>
</tr>
<tr>
<td>Time elapsed from ingestion to the beginning of hemoperfusion, h</td>
<td>9.9 ± 8.0</td>
<td>8.4 ± 4.5</td>
<td>0.3483</td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
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<th>Control Group (n = 28)</th>
<th>Study Group (n = 22)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>26.8 ± 10.1</td>
<td>28.2 ± 11.1</td>
<td>0.6952</td>
</tr>
<tr>
<td>Sex</td>
<td>18 M, 10 F</td>
<td>13 M, 9 F</td>
<td>0.7742</td>
</tr>
<tr>
<td>Time elapsed from ingestion to arrival at ER, h</td>
<td>5.9 ± 5.4</td>
<td>5.1 ± 4.8</td>
<td>0.8426</td>
</tr>
<tr>
<td>Time elapsed from ingestion to the beginning of hemoperfusion, h</td>
<td>8.5 ± 5.5</td>
<td>7.6 ± 4.9</td>
<td>0.3483</td>
</tr>
<tr>
<td>Time elapsed from ingestion to the time of urine PQ tests, h</td>
<td>6.4 ± 6.7</td>
<td>5.6 ± 4.8</td>
<td>0.5811</td>
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<tr>
<td>Severity of PQ poisoning</td>
<td>9 NB, 19 DB</td>
<td>8 NB, 14 DB</td>
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<tr>
<td>Acute renal failure</td>
<td>20/28 (71.4%)</td>
<td>15/22 (68.2%)</td>
<td>0.9999</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>2.9 ± 1.0</td>
<td>2.1 ± 1.3</td>
<td>0.8704</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>3/28 (10.7%)</td>
<td>3/22 (13.6%)</td>
<td>0.9999</td>
</tr>
<tr>
<td>Arterial blood PaO₂ at room air, mm Hg</td>
<td>87.2 ± 15.7</td>
<td>85.5 ± 14.7</td>
<td>0.6916</td>
</tr>
<tr>
<td>Mortality</td>
<td>16/28 (57.1%)</td>
<td>4/22 (18.2%)</td>
<td>0.0084</td>
</tr>
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</table>

Definition of abbreviations: DB = dark blue color; ER = emergency room; NB = navy blue color in sodium dithionite urine test.

*p < 0.05 indicates significant differences between variables in Student's t test and chi-square test with Fisher exact test.
lower than that of the control group (16 of 28, 57.1%; chi-square test, p = 0.0052; corrected by Fisher test, p = 0.0084). All fatalities in these two groups were caused by progression of respiratory failure. The pulse therapy group included eight patients (8 of 22, 36.4%) with leukopenia (white blood cell count [WBC] < 3,000), which was considered to be a side effect of pulse therapy. They spontaneously recovered 1 wk later without mortality. Leukopenia was the only major complication. Other complications, including hair loss and acne, were noted in some patients after pulse therapy.

**DISCUSSION**

Our results, similar to our preliminary report (15), suggest that pulse therapy with CP and MP may improve the survival rate of patients with moderate to severe PQ poisoning. However, our preliminary report was not a prospective study and only included a small number of patients. The current prospective, controlled study with a large group of patients may yield a more definite conclusion in treatments for PQ poisoning.

Comparison to previous studies (11, 12), excluding patients with fulminant paraquat poisoning from our study, clarifies the efficacy of pulse therapy in treating patients with moderate to severe paraquat poisoning. This may be the reason why our study demonstrated greater efficacy than others. In addition, the pulse therapy may also have improved the survival rate of our patients, although the exact mechanism is unknown. In a previous work (16) which was confirmed by a subsequent study (17), we found that the respiratory function and arterial blood oxygen concentrations of PQ-poisoned survivors with lung fibrosis could gradually improve to nearly normal after 3 mo follow-up, even if the lung fibrosis persisted. Hence, the severe inflammation, not the fibrosis, of lung may play the predominant role in the lethal hypoxia of patients with PQ poisoning during the subacute period of intoxication. If the PQ-induced lung inflammation can be attenuated, the survival rate of PQ intoxication may be improved, especially in patients with moderate to severe PQ poisoning. Pulse therapy with MP is known as a strong anti-inflammation treatment in clinical practice (13, 14). CP exerts a wide range of immunomodulatory effects that influence virtually all components of the cellular and humoral immune response and reduce the severity of inflammation (18). In addition, CP-induced leukopenia may contribute to reduce pulmonary inflammatory changes of PQ-poisoned patients (11). Hence, the efficacy of pulse therapy may be due to improvement of the PQ-induced severe inflammatory changes of lungs and reduction of the severity of hypoxia. Although CP may induce pulmonary toxicity in clinical practice, the frequency is only 1% or less (19) and most reports are from patients with malignant disease who received multiple agents (20). There were no severe complications in the study group patients, which suggests that the pulse therapy is safe and well tolerated.

Lack of plasma PQ level in our patients is the limitation of this study, but the plasma PQ level falls very quickly after poisoning; an error of an hour or two in the estimate of time of ingestion can move a patient from the 30% to the 70% survival curve (21). In addition, practical experience suggests that such inaccuracies are not uncommon (21). Because previous studies (5–7) showed that plasma and urine tests within the first 24 h of intoxication were good predictors of outcome and prognosis, the urine dithionite test is a reasonable indicator of the severity of PQ poisoning of our patients. In addition, it can be performed easily and quickly in any situation and no specific equipment is needed.

In conclusion, our results demonstrate that pulse therapy with CP and MP may be effective in treating patients with moderate to severe PQ poisoning, but not in treating patients with fulminant PQ poisoning. Further double-blind controlled studies are required to confirm this observation.

**References**