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Prolonged methylprednisolone therapy after the pulse treatment for patients with moderate-to-severe paraquat poisoning

A retrospective analysis

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Abstract

This retrospective study aims to evaluate the effect of prolonged methylprednisolone (MP) therapy on the mortality of patients with moderate-to-severe paraquat (PQ) poisoning after the pulse treatment.

We performed a retrospective analysis of patients with acute moderate-to-severe PQ poisoning that were admitted to the emergency department from May 2012 to August 2016. Out of 138 patients, 60 were treated with pulse treatment (15 mg kg^{-1} day^{-1} MP for 3 days) and 78 were treated with prolonged MP therapy after pulse treatment (15 mg kg^{-1} day^{-1} MP for 3 days; afterward, the dosage was reduced in half every 2 days, and the MP therapy was terminated until 0.47 mg kg^{-1} day^{-1}). Kaplan–Meier method was used to compare the mortality between the 2 groups. Cox proportional hazard models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI).

The mortality of the prolonged MP therapy after pulse treatment group was lower than that of the pulse group (47.4% vs 63.3%; log-rank tests, $P = .003$). According to the multivariate Cox analysis, the prolonged MP therapy after pulse treatment was significantly associated with a lower mortality risk (HR: 0.31, 95% CI: 0.19–0.52, $P < .001$) compared with the pulse group. In addition, the prolonged MP therapy after pulse treatment caused more incidences of leucopenia than the pulse treatment alone (25.6% vs 11.7%, $P = .04$).

The prolonged MP therapy after pulse treatment can reduce the mortality of moderate-to-severe PQ poisoning patients.

Abbreviations: CI = confidence intervals, HR = hazard ratios, MP = methylprednisolone, PQ = paraquat.

Keywords: lung injury, methylprednisolone, mortality, paraquat

1. Introduction

Paraquat (PQ) (1,1′-dimethyl-4,4′-bipyridinium dichloride) is a nonselective contact herbicide widely used in many countries since 1960s. Given its selective accumulation in the lungs, PQ causes severe lung injury, which manifests in edema, hemorrhage, interstitial inflammation, and progressive fibrosis. Globally, 250,000 to 370,000 people die from pesticide poisoning each year, and more than 90% of the individuals with acute poisoning attempted to commit suicide by intentionally ingesting PQ.[1]

When administered early in the course of poisoning, the combined glucocorticoid and cyclophosphamide pulse therapy shows promising results in reducing the life-threatening respiratory complications caused by the moderate-to-severe PQ poisoning.[2] Some reports indicated a high efficacy of prolonged glucocorticoid therapy after pulse treatment.[3–6] However, limited information is found in literature about the cases of PQ poisoning. The use of prolonged glucocorticoid after pulse treatment for PQ poisoning is still considered an experimental therapy; thus, the beneficial effects of its prolonged administration require further validation. Therefore, we designed a retrospective study to evaluate the effect of prolonged MP therapy after pulse treatment on the mortality of patients with moderate-to-severe PQ poisoning.

2. Methods

2.1. Ethics and consent

This retrospective study complied with the guidelines of the Declaration of Helsinki and was reviewed and permitted by the Institutional Ethics Committee of Cangzhou Central Hospital, Hebei, China. The need for individual consent was waived off by the committees because of the retrospective review of the existing data. However, informed consents regarding the risks associated with acute PQ poisoning and all treatment modalities (particularly charcoal hemoperfusion) were obtained from all patients upon their initial admission.

2.2. Study design and patients

We retrospectively reviewed the medical records of 138 patients with acute moderate-to-severe PQ poisoning that were admitted

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Table 1

General information of the 2 groups upon hospital admission.

	Pulse group (n = 60)	Prolonged therapy after pulse treatment group (n = 78)	*P*
Age, y	38.42 ± 10.36	35.29 ± 11.50	.101
Gender, male/female	21/39	30/48	.676
Smoking history, yes/no	17/43	20/58	.723
Time from ingestion to arrival, h	4.12 ± 1.27	3.79 ± 1.19	.121
PaO_2 at room air upon arrival, mm Hg	94.00 (2.00)	94.00 (1.00)	.115
Serum ALT upon arrival, U/L	33.50 (16.00)	34.50 (13.00)	.420
Serum creatinine upon arrival, mg/dL	115.00 (73.50)	110.50 (67.00)	.652

ALT = alanine aminotransferase, PaO_2 = alveolar oxygen partial pressure.

to the Emergency Ward from May 2012 to August 2016. The dithionite reaction in urine samples was used to select the patients with moderate-to-severe poisoning at the time of presentation. The presence of a navy blue or dark blue color in the urine samples indicates the moderate-to-severe poisoning.[7] The label of a pesticide bottle shows a variety of toxicants. Subsequently, the information listed on the bottle label is used to identify the types of poisons ingested by patients. If a bottle had no label, the relatives of patients are instructed to send samples of the poisonous substance and serum for toxicology analyses.

2.3. Inclusion and exclusion criteria

Inclusion criteria were as follows: presents PQ poisoning by oral intake; aged >14; and admission is within 8 hours of PQ poisoning. Exclusion criteria were as follows: with dermal or intravascular exposure; combination with other types of poisoning; with history of severe diseases of the heart, lung, liver, kidney, or hematological system; with multiple organ failure; pregnant or lactating; or with cancer.

2.4. Grouping and treatment

Eligible patients were divided into 2 groups. Patients in the pulse treatment group received 15 $mg\,kg^{-1}\,day^{-1}$ MP for 3 days.[8,9] Patients in the prolonged MP therapy after pulse treatment group received 15 $mg\,kg^{-1}\,day^{-1}$ MP for 3 days; the dosage was subsequently reduced in half every 2 days, and MP therapy was terminated until 0.47 $mg\,kg^{-1}\,day^{-1}$. Out of 138 patients, 60 were treated with pulse treatment and 78 were treated with prolonged MP therapy after pulse treatment. All patients received conventional therapy, which included gastric lavage, catharsis, fluid supplement, cyclophosphamide (15 $kg^{-1}\,day^{-1}$ up to 2 days), diuresis, hemoperfusion (HP) (upon admission, all patients immediately received 1–3 courses of 3 hours active charcoal containing HP therapy based on the result of urine PQ detection and clinical condition), antibiotic treatment to prevent infection, and organ-support therapy. In order to calculate the survival time, the starting point was identified as the date of PQ poisoning by oral intake, and all patients were followed up for 3 months or until death. Survival time was checked from medical records or telephone follow-up.

2.5. Data collection

The data provided by the patients were collected by 2 well-trained physicians (Jie Gao and Shunyi Feng) using a standard data-collection form. Data included the age, sex, time from ingestion to arrival, PaO_2 at room air upon arrival, serum creatinine upon arrival, serum alanine aminotransferase upon arrival, and smoking history.

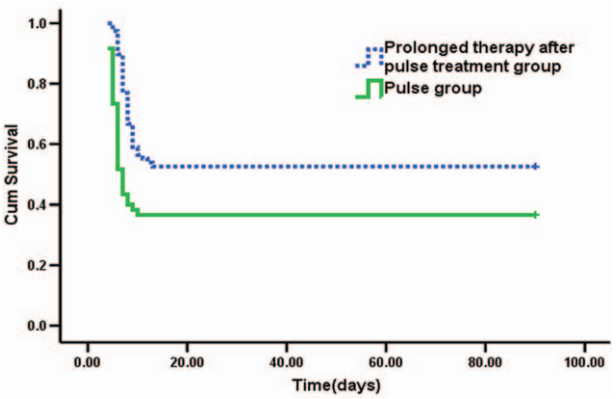

Figure 1. Kaplan–Meier analysis of survival curves between the 2 groups during the study.

2.6. Statistical analysis

Statistical analyses were conducted using SPSS version 13.0 (SPSS, Inc., Chicago, IL). The independent sample *t* test was used to evaluate the measurement data. If a normal distribution was followed, the data were presented as mean ± standard deviation; otherwise, 2-independent sample nonparametric tests were performed, and the data were presented as median ± interquartile range. Survival rates were analyzed using Kaplan–Meier method and were compared using log-rank test. Cox proportional hazard models were used to assess the effect of covariates (age, gender, smoking history, time from ingestion to arrival, PaO_2 at room air upon arrival, serum alanine aminotransferase upon arrival, and serum creatinine upon arrival) on the mortality. Estimated risks of death were reported as hazard ratios (HR) with 95% confidence intervals (CI). Categorical data were analyzed using chi-square test. Statistical significance was considered at $P < .05$.

3. Results

Out of 138 patients, 60 were treated with pulse treatment and 78 were treated with prolonged MP therapy after pulse treatment. The pulse treatment and prolonged MP therapy after pulse treatment groups showed no significant differences on their clinical features collected upon admission (Table 1). The overall mortality was 54.3% (75/138). The overall mortality rates for the pulse group and the prolonged MP therapy after pulse treatment group were 47.4% and 63.3%, respectively. Statistically significant differences were observed in the mortality using Kaplan–Meier method with log-rank analysis (log-rank test, $P = .003$; Fig. 1). The clinical features collected upon admission were evaluated by multivariate Cox analysis (Table 2). Prolonged MP therapy after pulse treatment was associated with a significantly lower mortality risk (HR: 0.31, 95% CI: 0.19–0.52, $P < .001$) than the pulse group.

In the prolonged MP therapy after pulse treatment group, 20 patients developed leucopenia (25.6%) and 5 (8.3%) developed fever. In the pulse group, 7 patients developed leucopenia (11%) and 8 (3.8%) developed fever. The prolonged MP therapy after treatment caused more incidences of leucopenia than the pulse

Table 2

Cox regression model.

	HR (95% CI)	P
Group	0.31 (0.19–0.52)	<.001
Time from ingestion to arrival	1.39 (1.09–1.78)	.008
Serum creatinine upon arrival	1.03 (1.02–1.04)	<.001
Age	1.02 (1.00–1.05)	.037

CI = confidence intervals, HR = hazard ratios.

treatment ($P = .04$). However, no signs of infection were noted in these patients. Hair loss was observed in 9 patients of the prolonged MP therapy after pulse treatment group (11.5%) and in 5 of the pulse treatment group (8.3%, $P = .506$); however, no treatment was required. In addition, acne developed in 10 patients of the prolonged MP therapy after pulse treatment group (12.8%) and in 5 of the pulse treatment group (8.3%, $P = .401$). However, the complication rapidly recovered after MP withdrawal.

4. Discussion

The present study provides further insights on the beneficial effects of prolonged MP therapy after pulse treatment on the overall mortality of patients with moderate-to-severe PQ poisoning. The overall survival rate was 54.3% (75/138) according to previous reports.[10] Multivariate analysis indicated that the age, time from ingestion to arrival, and serum creatinine upon arrival were independently associated with mortality, whereas prolonged MP was associated with protective factors.

In 2014, Yu et al[6] described a case report of acute severe PQ poisoning with long-term follow-up and found that the pulmonary damage was aggravated when the patient stopped taking glucocorticoid; however, the patient recovered again after the glucocorticoid treatment. They designed a nationwide large-scale population-based retrospective cohort study to investigate the effect of PQ poisoning with immunosuppressive treatment and found that the group with prolonged glucocorticoid therapy showed a significantly higher number of survival days than the pulse group.[11] Moreover, Chen et al[12] reported that the prolonged glucocorticoid treatment increases the surfactant pool size and improves the lung histology of PQ-injured lungs. These results support our study. By contrast, Perriëns et al[13] failed to find any significant difference in the respiratory failure. However, most of these reports were conducted in a single institution with small sample sizes and nonrandomized studies. Therefore, drawing firm conclusions regarding their outcomes is difficult.

Adequate dose and duration of MP for treatment of patients with PQ poisoning is a major issue in PQ research. Earlier studies[14–16] involved a dexamethasone administration of 24 mg day^{-1} for 2 weeks, followed by 1.5 mg day^{-1} for another 2 weeks; whereas an MP administration of 1 g kg^{-1} for 3 days, followed by dexamethasone 1.5-30 mg day^{-1} for 1 to 2 weeks,[4,17,18] is currently recommended for PQ intoxication. A recent meta-analysis[19] confirmed that the pulse therapy with a MP dose of 1 g for 3 days is safe and well-tolerated. In addition, some recent trials[3,9] showed a novel method: initial pulse therapy with methylprednisolone (MP) (1 g day^{-1} for 3 days), then dexamethasone 20 mg day^{-1} until PaO_2 was 80 mm Hg, and repeated pulse therapy with MP (1 g day^{-1} for 3 days), which was repeated if PaO_2 was <60 mm Hg. The results of the present study confirmed that the novel therapy reduces the mortality of patients with severe PQ poisoning. However, the limitations of this study include the lack of a placebo control group and the relatively small sample size of the control group, which might limit the generalizability of the study findings to other patients with severe PQ poisoning. Hence, the adequate dose and duration of MP for the treatment of patients with PQ poisoning are not yet determined.

The efficacy of HP in clearing serum PQ depends on the function of the HP cartridge and plasma levels. Some studies[20,21] reported that the peak time of plasma PQ is 1 to 3 hours, whereas the peak time of lung cells is approximately 4 to 5 hours. Within 5 to 6 hours after ingestion, 90% of PQ disappears in the plasma. The reduction rate of PQ by HP is 67% to 83% in 3 hours, which shows high efficacy throughout the HP in all subjects, according to a report by Hong et al.[20] Hampson et al[22] and Pond et al[23] reported the effectiveness of charcoal HP and hence should be continuously administered for 6 to 8 hours. Although increasing HP time alone might improve the overall clearance rate of HP on plasma PQ, the elimination efficiency of HP would be decreased as time went on. Thus, plasma monitoring or urinary PQ concentration monitoring may be conducted to optimize HP therapeutic time for patients with PQ poisoning.[24,25] Upon admission, all patients immediately received 1 to 3 courses of 3 hours active charcoal containing HP therapy based on the result of urine PQ detection and clinical condition in our department. The dithionite urine test was conducted half an hour before the end of each course of 3 hours charcoal HP therapy; if negative, HP therapy was stopped.

Our study encountered several limitations. First, we did not measure the plasma PQ levels, which had a higher predictive value than urine data using the colorimetric test. However, urine data contribute to a rapid evaluation of prognosis.[26] Second, this single-center, retrospective study included data from a relatively small number of patients. Therefore, the findings need further verification in a large-scale, multicenter, randomized, and controlled study. Finally, the authors acknowledged that the study was limited by its retrospective design and potential recall bias with an inability to recall the accurate death time.

In conclusion, prolonged MP therapy after pulse treatment reduces the overall mortality of patients with moderate-to-severe PQ poisoning. However, the dosage and prolonged time still need further investigation from large-scale and multicenter clinical trials.

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