Kidney Res Clin Pract 35 (2016) 102–106

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Original Article

Predicting the probability of survival in acute paraquat poisoning☆

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Article history:
Received 1 October 2015
Received in revised form
24 January 2016
Accepted 31 January 2016
Available online 27 February 2016

Keywords:
Creatinine
Logistic models
Paraquat
Prognosis

Abstract

Background: Paraquat (PQ) concentration–time data have been used to predict prognosis for 3 decades. The aim of this study was to find a more accurate method to predict the probability of survival.

Methods: This study included 788 patients with PQ poisoning who were diagnosed using plasma PQ concentration between January 2005 and August 2012. We divided these patients into 2 groups (survivors vs. nonsurvivors), compared their clinical characteristics, and analyzed the predictors of survival.

Results: The mean age of the included patients was 57 years (range, 14–95 years). When we compared clinical characteristics between survivors (n = 149, 19%) and nonsurvivors (n = 639, 81%), survivors were younger (47 ± 14 years vs. 59 ± 16 years) and had lower plasma PQ concentrations (1.44 ± 8.77 μg/mL vs. 80.33 ± 123.15 μg/mL) than nonsurvivors. On admission, serum creatinine was lower in survivors than in nonsurvivors (0.95 ± 0.91 mg/dL vs. 1.88 ± 1.27 mg/dL). In multivariate logistic regression analysis, age and logarithmically converted serum creatinine [ln(Cr)], [ln(time)], and [ln(PQ)] were assessed as prognostic factors to predict survival in PQ poisoning. The predicted probability of survival using significant prognostic factors was exp (logit)/[1 + exp(logit)], where logit = −1.347 + [0.212 × sex (male = 1, female = 0)] + (0.032 × age) + [1.551 × ln(Cr)] + [0.391 × ln(hours since ingestion)] + [1.076 × ln(plasma PQ μg/mL)]. With this equation, the sensitivity and specificity were 86.5% and 98.7%, respectively.

Conclusion: Age, ln(Cr), ln(time), and ln(PQ) were important prognostic factors in PQ poisoning, and our equation can be helpful to predict the survival in acute PQ poisoning patients.

Introduction

Paraquat (PQ; 1,1'-dimethyl-4,4'-bipyridinium) dichloride is a nonselective herbicide that has been widely used in many countries since the 1960s. It has unique properties which make it important to agriculture; it is a fast-acting broad-spectrum contact weedkiller which is very rainfast and is deactivated on contact with soil. However, ingestion of the concentrated formulation is very toxic to humans with no specific antidote or

☆ The authors alone were responsible for the content and writing of the paper.

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http://dx.doi.org/10.1016/j.krcp.2016.01.003

conclusively effective treatment demonstrated [1]. PQ has been used for the past 3 decades in Korea, with an estimated 2,000 toxic ingestions annually [2]. Because there are few effective treatments for the management of PQ poisoning, it is important to predict patient mortality. Early prediction of inevitable death would allow the cessation of inappropriate treatments in acute PQ poisoning [3].

The prognosis of acute PQ poisoning is dependent on the plasma PQ concentrations, and PQ concentration−time data have been used to predict outcomes for 3 decades [4]. Because a nomogram was introduced to relate the patient outcome to the plasma PQ level and the time from poisoning to blood sampling, other graphs and formulas have been reported [5−9]. However, these studies involved small sample sizes and were better at predicting death than survival [10]. Recently, biomarkers such as pentraxin-3 or neutrophil gelatinase−associated lipocalin were used to predict the prognosis in patients with PQ poisoning [11,12].

Therefore, we investigated prognostic factors affecting survival in patients with PQ poisoning and estimated the predicted probability of survival through logistic regression analysis using plasma PQ concentration, time since ingestion, and other variables.

Methods

Patient selection

Eight hundred ten patients who had ingested PQ visited our hospital between January 2005 and December 2012. We excluded 22 patients who were transferred to other hospitals during treatment or otherwise lost to follow-up. Therefore, 788 patients were included in this study and were divided into 2 groups: survival ($n = 149$) and nonsurvival ($n = 639$). Patients who lived for more than 3 months were included in the survival group. This study was approved by the Institutional Review Board of Presbyterian Medical Center.

Data collection and study variables

Physicians treated the patients and recorded all the information on a standardized data collection form. Standardized medical emergency procedures were conducted according to the Presbyterian Medical Center protocol for PQ poisoning (Table 1). Briefly, gastric lavage was performed, and 100 g of Fuller's earth in 200 mL of 20% mannitol was given if poisoning had occurred within the previous 12 hours. Hemoperfusion was performed if a urinary PQ test was positive within 24 hours. Urinary PQ was checked semiquantitatively with the dithionite method on arrival [13]. These results were presented as Grades 1–4, where black = + 4, deep blue = + 3, light blue = + 2, and barely distinguishable blue = + 1.

We developed 3 models to predict survival according to the interval after ingestion and initial creatinine. Model 1 was based on the initial plasma PQ concentration and time since ingestion. Model 2 was based on adding of prognostic factors to predict the survival of the patients with PQ poisoning in our study to Model 1. Model 3 was based on a 2-hour PQ level instead of the initial PQ level.

Table 1. Summary of treatment guidelines for acute paraquat intoxication

1. Gastric lavage
2. Dithionite urine test
3. Fuller's earth, 100 g in 200-mL mannitol
4. A. Antioxidant (intravenous administration)
Vitamin B and E
B. For renal preservation
Furosemide
15% mannitol
5. Emergency hemoperfusion
6. Key laboratory parameters
Blood chemistry: blood urea nitrogen, creatinine, amylase, lipase
Electrolyte: Na, K, Cl
Arterial blood gas analysis
Plasma paraquat level

Examination of plasma PQ concentration

Blood samples for the measurement of plasma PQ concentration (PQ 0 hour) were collected as soon as patients arrived at the emergency department. Samples were centrifuged at 1,600 × *g* for 15 minutes at 4°C and analyzed at the Christian Medical Research Center. If patients arrived within 4 hours of ingestion, another blood sample (PQ 2 hours) was collected 2 hours later. PQ levels were measured using high-performance liquid chromatography.

Statistical analysis

All data are presented as mean ± standard deviation unless otherwise specified. Differences in covariates between survivors and nonsurvivors were tested with the Student *t* test for continuous variables and the chi-square test for categorical variables. Multiple logistic regression analysis was applied to predict the outcome after acute PQ poisoning. In this study, time since ingestion (in hours), serum creatinine, and plasma PQ level were used in multiple logistic regression analysis after logarithmic conversion as they did not display a normal distribution. To determine the sensitivity and specificity of the prediction equation, receiver operating characteristic curves were generated. A P value of < 0.05 was considered statistically significant. Statistical analysis was carried out using SPSS software, version 21 (IBM corporation, New York, NY, USA) and MedCalc 12.5 (MedCalc Software bvba, Mariakerke, Belgium).

Table 2. Clinical and laboratory findings of the 788 patients with PQ poisoning

Characteristics	
Age (y)	57 ± 16
Male	507 (64)
Time since ingestion (h)	6.6 ± 15.0
Hemoperfusion therapy	594 (75)
Serum creatinine (mg/dL)	1.7 ± 1.3
Serum alanine aminotransferase (IU/L)	36 ± 50
Serum lipase (IU/L)	103 ± 184
P_{CO_2} (mmHg)	25.0 ± 9.1
HCO_3 (mmol/L)	14.8 ± 6.8
Amount of PQ ingested (mL)	151 ± 124
Plasma PQ 0-h level (μg/mL)	65 ± 115
Plasma PQ 2-h level (μg/mL)*	41 ± 80
Urine PQ test	
Negative	30 (3.8)
Weakly positive	84 (10.6)
Positive	44 (5.6)
Strong positive	632 (80)

Data are presented as mean ± SD or number (%).
* The data are available in 379 patients.
PQ, paraquat.

Table 3. Comparison of clinical characteristics between survivors and nonsurvivors

	Survivor ($n = 149$)	Nonsurvivor ($n = 639$)	P
Age (y)	47.0 ± 14.0	59.0 ± 16.0	< 0.012
Male	83 (56)	422 (67)	0.233
Time since ingestion (h)	8.7 ± 17.2	6.1 ± 14.4	0.094
Hemoperfusion therapy	141 (95)	453 (71)	< 0.015
Serum creatinine (mg/dL)	1.0 ± 0.9	1.9 ± 1.3	< 0.012
Serum alanine aminotransferase (IU/L)	32.0 ± 34.0	37.0 ± 53.0	0.230
Serum lipase (IU/L)	46.0 ± 38.0	115.0 ± 200.0	< 0.010
P_{CO_2} (mmHg)	30.0 ± 7.0	23.0 ± 9.0	< 0.011
HCO_3 (mmol/L)	19.0 ± 14.0	13.0 ± 7.0	< 0.012
Amount of PQ ingested (mL)	34.0 ± 22.0	178.0 ± 122.0	< 0.014
Plasma PQ 0-h level (μg/mL)	0.4 ± 0.7	80.3 ± 123.1	< 0.010
Plasma PQ 2-h level (μg/mL)	0.2 ± 0.3*	58.9 ± 102.1†	< 0.013
Urine PQ test			< 0.010
Negative	26 (17)	4 (1)	
Weakly positive	69 (46)	15 (2)	
Positive	30 (20)	14 (2)	
Strong positive	24 (16)	606 (95)	

Data are presented as mean ± SD or number (%).
* The data are available in 82 patients.
† The data are available in 297 patients.
NS, not significant; PQ, paraquat.

Results

Baseline characteristics

The baseline characteristics of the 788 patients are presented in Table 2. Of the study participants, 507 (64%) were male. The mean time since ingestion was 6.6 hours, and 594 patients (75%) received hemoperfusion therapy. The initial mean serum creatinine and lipase levels were 1.71 mg/dL (range, 0.1–10.6 mg/dL) and 103 IU/L (range, 8–1,944 IU/L), respectively. The mean P_{CO_2} and bicarbonate levels were 25 mmHg (range, 3–56 mmHg) and 14.8 mmol/L (range, 2–35 mmol/L), respectively. The mean ingested amount of PQ as estimated with history was 151 mL (range, 5–600 mL), and the initial mean plasma PQ level on admission was 65.23 μg/mL (range, 0.5–833 μg/mL). Of 525 patients who arrived within 4 hours of ingestion, 1 more sample was collected 2 hours later in 379 patients (72.2%), and, of 758 patients (96.2%) in whom a urine dithionite test was performed, 632 patients (83%) showed strong positive results. Of 788 patients, 149 patients (19%) survived.

Comparison of clinical characteristics between survivors and nonsurvivors

When we compared clinical characteristics between survivors ($n = 149$) and nonsurvivors ($n = 639$), the survivors were younger (47 ± 14 years vs. 59 ± 16 years) and had lower serum creatinine on admission (0.95 ± 0.91 mg/dL vs. 1.88 ± 1.27 mg/dL; Table 3). Survivors also had lower plasma PQ concentrations (0.44 ± 0.70 μg/mL vs. 80.48 ± 123.13 μg/mL; Table 3). Although survivors had a lower amylase level than that of nonsurvivors, there was no difference in serum alanine aminotransferase between the 2 groups. The proportion of positive or strong positive urine tests was much higher in nonsurvivors than in survivors (Table 3).

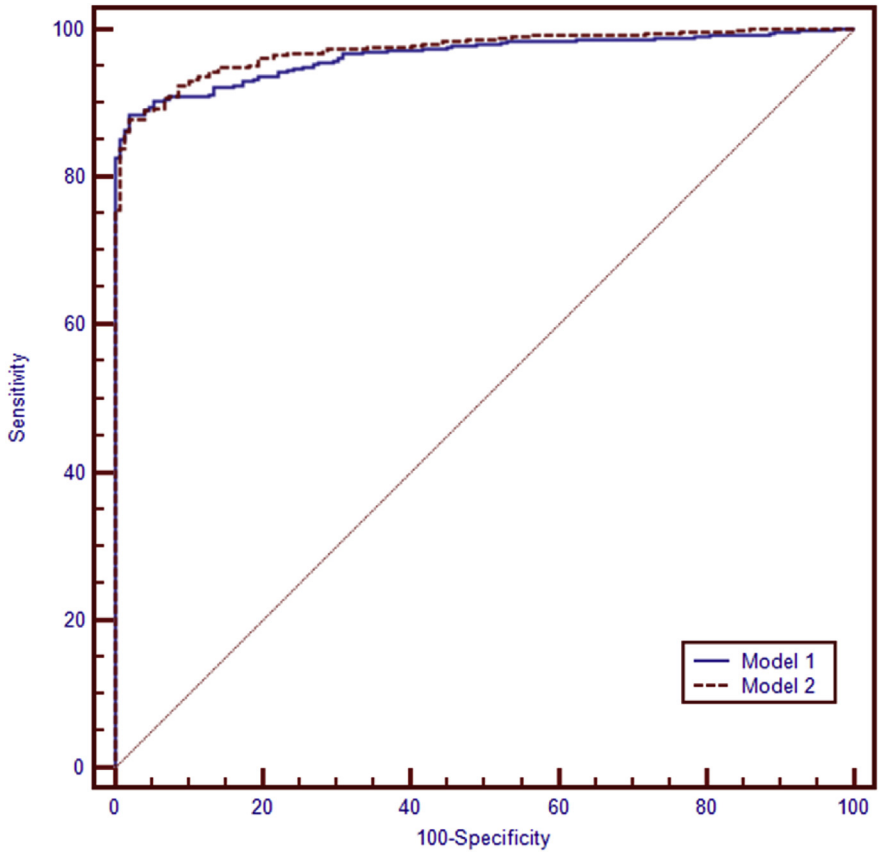

Figure 1. Comparison of receiver operating characteristic analysis of models using logistic regression. The sensitivity and specificity of Models 2 and 3 are better than those of Model 1. The curve of Model 2 is very close to that of Model 3, which is not shown in this figure.

Table 4. Univariate logistic regression analysis

Variables	Relative risk	95% Confidence interval		P
Age (y)	1.046	1.033	1.058	< 0.011
Male	1.546	1.076	2.222	0.018
ln(time)	0.820	0.515	1.307	0.405
HP	0.139	0.067	0.290	< 0.012
ln(Cr)	20.132	11.374	35.639	< 0.010
Serum ALT (IU/L)	1.004	0.998	1.010	0.204
Serum lipase (IU/L)	1.010	1.009	1.023	< 0.011
P_{CO_2} (mmHg)	0.912	0.898	0.939	< 0.012
HCO_3 (mmol/L)	0.821	0.804	0.866	< 0.013
ln(PQ)	2.648	2.271	3.087	< 0.011

ALT, alanine aminotransferase; Cr, creatinine; HP, hemoperfusion; PQ, paraquat.

Table 5. Multivariate logistic regression analysis

Variable	B	Relative risk	95% Confidence interval	P
Age (y)	0.032	1.271	1.012–1.053	0.010
ln(Cr)	1.551	4.721	2.553–8.715	< 0.001
ln(time)	0.391	1.478	1.048–2.085	0.032
ln(PQ)	1.076	2.932	2.406–3.573	< 0.001

Cr, creatinine; PQ, paraquat.

Prediction of survival in patients with PQ poisoning

The equation for the predicted probability of survival was exp (logit)/[1 + exp(logit)]. When time since ingestion and PQ 0-hour level were used, the equation was as follows: logit = 0.006 + [1.519 × ln(time)] + [2.444 × ln(PQ 0 hours)] (Model 1; Fig. 1). The sensitivity and specificity were 86.1% and 96.6%, respectively. We assessed age and logarithmically converted creatinine [ln(Cr)], time [ln(time)], and PQ 0-hour level [ln(PQ 0 hours)] as prognostic factors to predict the survival of the patients with PQ poisoning (Tables 4 and 5). When we added these prognostic factors such as ln(Cr), ln(time), and ln(PQ 0 hours) to Model 1, the predicted probability of survival was exp (logit)/[1 + exp(logit)], where logit = −1.347 + [0.212 × sex (male = 1, female = 0)] + (0.032 × age) + [1.551 × ln(Cr)] + [0.391 × ln(time)] + [1.076 × ln(PQ)] (Model 2; Fig. 1). Using this logistic regression analysis, the sensitivity and specificity of Model 2 were 86.5% and 98.7%, respectively. Of 525 patients who arrived within 4 hours of ingestion, one more sample was collected 2 hours later in 379 patients (72.2%), we used the available 2-hour PQ level (PQ 2 hours) instead of the initial PQ level (PQ 0 hours; Model 3). The sensitivity and specificity were 88.7% and 98.0%, respectively (Table 6). However, there was no statistical difference between the 2 methods (Models 2 vs. 3, or PQ 0 hours vs. PQ 2 hours). However, these 2 methods showed better sensitivity and specificity than Model 1, in which only time [ln(time)] and PQ level [ln(PQ 0h)] were included.

Discussion

The survival rate was 19% in our study. When compared with nonsurvivors, survivors were younger and showed better renal function on admission. The mean plasma PQ level was lower in survivors than in nonsurvivors. Age, ln(Cr), ln(time), and ln(PQ) predicted survival in patients with PQ poisoning. We calculated the predicted probability of survival using significant prognostic factors after adjusting for sex.

PQ is a nonselective, fast-acting herbicide that is environmentally harmless because of its rapid decomposition into nontoxic compounds after soil contact [1]. However, it is highly toxic to humans, and the mortality of PQ poisoning ranges from 50% to 90% [4]. In Korea, the mortality rate was reported as 70.7% and 62% by 2 different investigators [14,15], which were slightly lower than what we observed (81%). This may be due to the higher PQ quantities ingested and subsequent higher PQ levels seen in our patients. We found that the proportion of patients with a strong positive test was larger than that reported by Lee et al (80% vs. 31.5%) [14].

Several parameters including liver enzymes, serum creatinine, potassium, arterial blood bicarbonate, respiratory index, and plasma and urinary PQ concentrations have been proposed as prognostic indications [4,14–19]. Measurement of plasma PQ concentration and its relationship to time from ingestion is very useful in assessing severity and predicting outcomes in PQ poisoning [5–7]. However, the prediction methods based on PQ concentration–time data are better at predicting death than survival [10]. It was reported that the sensitivity and specificity of previous formulas ranged from 58% to 81% and from 83% to 96%, respectively [10].

We calculated the predicted probability of survival with time and concentration as variables. The sensitivity and specificity of our equation were 86.1% and 96.6%, respectively, when only time and PQ concentration were included in the equation. However, after adjustment for sex, we included age, ln(Cr), ln(time), and ln(PQ). The equation was exp (logit)/[1 + exp(logit)], where logit = −1.347 + [0.212 × sex (male = 1, female = 0)] + (0.032 × age) + [1.551 × ln(Cr)] + [0.391 × ln(time)] + [1.076 × ln(PQ)]. The sensitivity and specificity of this equation were increased to 86.5% and 98.7%, respectively, which were higher than those of the equation using only time and concentration. Therefore, we believe that our equation could be helpful to predict the survival in acute PQ poisoning patients. Furthermore, accurate prediction of survival can be useful to decide the treatment strategy in patients with PQ poisoning.

Some data suggest that the plasma PQ concentration peaks within 2–4 hours of ingestion, with a distribution half-life of 5 hours [20]. Therefore, it is likely that plasma PQ concentrations checked later (at least at 4 hours after ingestion) yield a better estimate of the total amount of PQ that has reached systemic circulation. In our study, 525 patients (66.7%) arrived

Table 6. Analysis of ROC curve

	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	AUC (95% CI)	
Model 1	0.861 (0.831–0.887)	0.966 (0.923–0.989)	0.991	0.618	0.957 (0.941–0.670)	Models 2, 3 > Model 1
Model 2	0.865 (0.836–0.891)	0.987 (0.952–0.998)	0.996	0.631	0.972 (0.958–0.982)	
Model 3	0.887 (0.860–0.911)	0.980 (0.942–0.996)	0.995	0.670	0.974 (0.960–0.984)	

AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

within 4 hours of ingestion. Of these, an additional sample was collected 2 hours later in 362 patients (68.9%). When we compared Models 1, 2, and 3, the areas under the receiver operating characteristic curve of Models 2 and 3 were larger than that of Model 1 (Table 3). The sensitivity and specificity of Models 2 and 3 were also better than those of Model 1; however, the differences between Models 2 and 3 were not significant. Therefore, this present study suggests that the addition of serum creatinine as a variable to the previous formula, which used only time and PQ level, can predict the survival more accurately in acute PQ poisoning. Previous reports have shown that renal function on admission was important in determining the prognosis of acute PQ poisoning [4,14,21]. Further studies may be required to determine whether PQ 0 hours or PQ 2 hours in patients who arrive within 4 hours of ingestion should be used in the equation.

Our study has some limitations. This is a retrospective study, and the study population comprised only Asian people. Although all patients received antioxidant therapy, some of the patients (25%) did not undergo hemoperfusion therapy in our study. In addition, we used PQ 2 hours as a variable in Model 3. However, we did not collect PQ 2 hours in all patients. Therefore, prospective randomized study is needed to predict the survival in PQ poisoning.

In conclusion, reliable predictors of prognosis can guide treatment and future clinical research on antidotes and therapies. In this study, the survival rate was 19%, and age, ln(Cr), ln(time), and ln(PQ) were the important prognostic factors in PQ poisoning. We calculated the predicted probability of survival using these variables, which had better sensitivity and specificity than those of previous studies. Therefore, our equation may be helpful in predicting mortality in acute PQ poisoning.

Conflicts of interest

All authors have no conflicts of interest to declare.

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