Toxicology Reports 1 (2014) 490–495

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Survival predictors in paraquat intoxification and role of immunosuppression

Keng-Hee Koh[a,b,*], Clare Hui-Hong Tan[a], Lawrence Wei-Soon Hii[a,c], Jun Lee[a], Laura Lui-Sian Ngu[a], Alvin Jung-Mau Chai[c], Chek-Loong Loh[d], Swee-Win Lam[e], Lily Mushahar[f], Tem-Lom Fam[b], Wan Shaariah Md Yusuf[f]

[a] Nephrology Unit and Department of Medicine, Sarawak General Hospital, Kuching, Malaysia
[b] Nephrology Unit and Department of Medicine, Miri Hospital, Malaysia
[c] Medical Department, Sibu Hospital, Malaysia
[d] Medical Department, Hospital Raja Permaisuri Bainun, Ipoh, Malaysia
[e] Medical Department, Hospital Sultan Abdul Halim, Sungai Petani, Malaysia
[f] Nephrology Department, Hospital Tuanku Ja'afar, Seremban, Malaysia

ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form 18 June 2014
Accepted 27 June 2014
Available online 18 July 2014

Keywords:
Paraquat poisoning
eGFR
Inflammation
Immunosuppression
Survival
Acute renal failure

ABSTRACT

Paraquat poisoning resulted in multiorgan failure and is associated with high mortality. We audited 83 historical cases of paraquat poisoning in past 2 years treated with conventional decontamination and supportive treatment, followed by enrolling 85 patients over a 2 year period into additional immunosuppression with intravenous (i.v.) methylprednisolone and i.v. cyclophosphamide.

Our results showed that age, poor renal function and leucocytosis are the main predictors of fatal outcome. Immunosuppression regime rendered higher survival (6 out of 17 patients (35.3%)) versus historical control (1 out of 18 patients (5.6%)) ($p = 0.041$) in the cohort with admission eGFR < 50 ml/min/1.73 m^2 and WBC count > 11,000/μL.

In contrast, there was no difference in survival with immunosuppression regime (38 out of 64 patients (59.4%)) compared to historical control (30 out of 52 patients (57.7%)) ($p = 0.885$) in those with eGFR > 50 ml/min/1.73 m^2 or WBC < 11,000/μL at presentation.

Multivariable logistic regression showed survival probability = exp(logit)/(1 + exp(logit)), in which logit = 13.962 − (0.233 × ln(age (year))) − (1.344 × ln(creatinine (μmol/L))) − (1.602 × ln(rise in creatinine (μmol/day))) − (0.614 × ln(WBC (,000/μL))) + (2.021 × immunosuppression) and immunosuppression = 1 if given and 0 if not. Immunosuppression therapy yielded odds ratio of 0.132 (95% confidential interval: 0.029–0.603, $p = 0.009$).

In conclusion, immunosuppression therapy with intravenous methylprednisolone and cyclophosphamide may counteract immune mediated inflammation after paraquat poisoning and improve survival of patients with admission eGFR < 50 ml/min/1.73 m^2 and WBC count > 11,000/μL.

* Corresponding author at: Department of Medicine, Miri Hospital, Jalan Cahaya, 98000 Miri, Malaysia. Tel.: +60 85 420033x251; fax: +60 85 416514.
E-mail addresses: kohkenghee@yahoo.com, kohkh@moh.gov.my, kohkenghee@gmail.com (K.-H. Koh).

http://dx.doi.org/10.1016/j.toxrep.2014.06.010

1. Introduction

Paraquat poisoning could result in multiorgan failure. Besides intestinal decontamination [1,2], the administration of glucocorticoids and cyclophosphamide has been advocated following the study by Lin et al. [3,4]. Because of constructive appraisal on the actual efficacy of immunosuppression [5], Lin et al. subsequently performed a randomized controlled trial of 23 patients with paraquat poisoning, with measurement of plasma paraquat levels. The study showed that the mortality rate was 31.3% in the treatment arm versus 85.7% in the control arm ($p = 0.0272$) [6]. Another study done in Iran showed similar trend in outcome [7] favouring the use of cyclophosphamide. Nevertheless, to our knowledge, there is not yet any study identifying the specific group that may benefit most from immunosuppression therapy. This in fact is an important piece of information, because one has to ascertain the potential benefit for each patient based on their clinical profile and decides the more suitable modality of treatment, whether to utilize larger dose of immunosuppression or to omit immunosuppression therapy.

2. Methods

This is a multicentre clinical trial performed in Ministry of Health Hospitals in Kuching, Miri, Sibu, Ipoh, Sungai Petani and Seremban cities.

The inclusion criteria were:

1. History of recent paraquat ingestion within 3 days prior to admission.
2. Positive urine paraquat test, or presence of any feature of systemic paraquat toxicity involving kidney, liver or lungs.

We excluded those subjects who were pregnant.

All patients were treated with intestinal decontamination (Appendix I) (23) and IV hydration. We enrolled 85 cases of paraquat poisoning in Years 2011 and 2012 into an immunosuppression protocol (Appendix II), comprising of IV methylprednisolone (1 g/day) for first 3 days (adjustment if needed in liver impairment) and IV cyclophosphamide (15 mg/kg/day) for first 2 days (adjustment if needed in acute kidney failure).

Their clinical profile and outcome were compared with historical cohort of 83 cases of paraquat poisoning in the past 2 years (Years 2009–2010).

This study was approval by Malaysian National Medical Research Ethical Committee (NMRR-11-587-9673) and informed consents were taken from patients. Outcome was verified by clinical notes and follow-up phone calls.

Paraquat was tested qualitatively with sodium bicarbonate and sodium dithionite. We estimated eGFR using the MDRD formula [10].

Our approaches in the analysis were:

a) Compare the clinical profile between subjects with immunosuppression therapy versus historical cohort.
b) Identify the predictors for survival.
c) Evaluate if these survival predictors affect the efficacy of immunosuppression in terms of survival.

The statistical data were analysed using Microsoft excel and SPSS 15 (Statistical Package for Social Science, SPSS Inc., Chicago, IL).

Only patients with complete data were included for analysis to derive the final output for statistical tables and figures.

Kolmogorov–Smirnov test was initially used to determine whether the data is in statistical normal distribution and subsequently logarithm transformation would be performed as necessary [11]. These would be followed by appropriate parametric or non-parametric test as well as parameter description: mean ± standard deviation.

Univariate analysis was performed with parametric test (e.g., Student's *t*-test, ANOVA) for survival comparison in data with statistical normal distribution and geometric transformation was performed as necessary. Factors that significantly affect the predictor and survival were analysed with ANCOVA test.

Chi square test and Fisher's exact test will be utilized according to the standard statistical procedure.

Finally we apply logistic regression to identify the risk predictors and use these factors to identify the patients that benefit best from immunosuppression.

3. Results

3.1. Comparison of baseline clinical parameters between the subjects with immunosuppression therapy and historical cohort

There were no significant differences in clinical parameters on admission between the two groups (Table 1).

3.2. Identification of survival predictors

Table 2 and Fig. 1A and B showed overall better survival in patients with higher eGFR (estimated glomerular filtration rate), low serum creatinine, slower creatinine rise, lower white blood cell (WBC) count, higher serum bicarbonate (HCO_3), besides traditional predictors of younger age and smaller amount of paraquat ingestion.

3.3. Evaluation of the efficacy of immunosuppression in groups with various survival predicting parameters

Comparing the two groups overall, there was mild survival benefit with 44 over 85 immunosuppression groups (52%), versus 38 over 83 historical controls survived (46%) ($p = 0.438$).

However, in cohort with eGFR < 50 ml/min/1.73 m^2 and WBC count > 11,000/μL at presentation, immunosuppression regime rendered significantly higher survival rate (6 out of 17 patients (35.3%)) when compared to historical control (1 out of 18 patients (5.6%)) ($p = 0.041$) (Fig. 2).

Nevertheless, there was no difference in survival with immunosuppression regime (38 out of 64 patients (59.4%)) compared to historical control (30 out of 52 patients