Association between liberal oxygen therapy and mortality in patients with paraquat poisoning: A multi-center retrospective cohort study

Xin-Hong Lin¹, Hsiu-Yung Pan¹,², Fu-Jen Cheng¹,², Kuo-Chen Huang¹, Chao-Jui Li¹, Chien-Chih Chen¹, Po-Chun Chuang¹*

¹ Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Niaosong Dist., Kaohsiung City, Taiwan (R.O.C.), ² Chang Gung University College of Medicine, Guishan District, Taoyuan City, Taiwan

* zhungboqun@gmail.com

Abstract

Paraquat (N, N’-dimethyl-4, 4’-bipyridinium dichloride, PQ) intoxication is a common cause of lethal poisoning. This study aimed to identify the risk of using liberal oxygen therapy in patients with PQ poisoning. This was a multi-center retrospective cohort study involving four medical institutions in Taiwan. Data were extracted from the Chang Gung Research Database (CGRD) from January 2004 to December 2016. Patients confirmed to have PQ intoxication with a urine PQ concentration \( \geq 5 \text{ ppm} \) were analyzed. Patients who received oxygen therapy before marked hypoxia (SpO2 \( \leq 90\% \)) were defined as receiving liberal oxygen therapy. The association between mortality and patient demographics, blood paraquat concentration (ppm), and liberal oxygen therapy were analyzed. A total of 416 patients were enrolled. The mortality rate was higher in the liberal oxygen therapy group (87.8\% vs. 73.7\%, \( P = 0.007 \)), especially in 28-day mortality (adjusted odds ratio [aOR]: 4.71, 95\% confidence interval [CI]: 1.533–14.471) and overall mortality (aOR: 5.97, 95\% CI: 1.692–21.049) groups. Mortality in patients with PQ poisoning was also associated with age (aOR: 1.04, 95\% CI: 1.015–1.073), blood creatinine level (aOR: 1.49, 95\% CI: 1.124–1.978), and blood paraquat concentration (ppm) (aOR, 1.51; 95\% CI: 1.298–1.766). Unless the evidence of hypoxia (SpO2 < 90\%) is clear, oxygen therapy should be avoided because it is associated with increased mortality.

Introduction

Paraquat (N, N’-dimethyl-4, 4’-bipyridinium dichloride; PQ) intoxication is a common cause of lethal poisoning in many parts of Asia, Oceania, and the Americas [1, 2]. For example, in Taiwan, 1811 patients were admitted with PQ intoxication from 1997 to 2009, with a mortality rate of 78.6\% [3]. Because paraquat is a nonselective, quick-acting, and cheap herbicide, it has been widely used in developing countries [4]. Paraquat is classified as a bipyridyl compound.
It's toxicity, which induces nonspecific cellular necrosis, occurs as a result of reactive oxygen species generation [6]. Once paraquat enters the intracellular space, it undergoes a process of alternate reduction and re-oxidation steps known as redox cycling.

Paraquat is oxidized to the paraquat radical upon entry into the cell and is subsequently reduced by enzyme systems such as (Nicotinamide adenine dinucleotide phosphate) NADPH-cytochrome P450 reductase and nitric oxide synthase to form a mono-cation (PQ$^+$) [7–9]. The PQ$^+$ is then rapidly re-oxidized to form the parent paraquat compound in the presence of O$_2$ and generates a superoxide radical (a reactive oxygen species). Reactive oxygen species has the characteristic of cytotoxicity that causes oxidative stress [10–13]. This leads to lipid peroxidation [14, 15], consumption of intracellular NADPH as long as NADPH and oxygen are available [16, 17], mitochondrial damage [18], and even apoptosis [19, 20].

Paraquat causes major organ damage, the most prominent being lung and kidney injuries, since high concentrations of the toxin were found in these organs [16, 21]. Most cases of paraquat ingestion induce poisoning, and the severity of toxicity is related to the dose ingested. The symptoms could be limited and topical if exposure is through dermal contact or through a spray. Lethal complications such as pneumonitis, pulmonary hemorrhage, and acute tubular necrosis could occur [16] if more than 10 mL of the solution (20% wt./vol) is ingested [21]. In previous in vivo studies, supplemental oxygen enhanced the toxicity of paraquat, which resulted in damage to alveolar cells, particularly the type II pneumocytes [22, 23]. In addition, the toxicity seemed to be correlated with the concentration of the oxygen supplied [24, 25]. In clinical practice, emergency physicians do not administer oxygen therapy in patients with acute PQ poisoning unless the patients are hypoxic (usually clinically defined as a pulse oximeter level < 90%) because of the concern that supplemental oxygen might exacerbate the toxicity of paraquat by enhancing the generation of reactive oxygen species [17]. Previous clinical studies have focused on the effects of immunotherapy and hemoperfusion to patients suffering from paraquat poisoning [26, 27]. We conducted a retrospective study to analyze the association between liberal oxygen therapy and the outcomes of PQ poisoning.

**Materials and methods**

**Ethics approval**

This retrospective study was approved by the Chang Gung medical foundation institutional review board (number 201901558B0). All patient data used in the analyses were anonymized and de-identified.

**Study setting**

The data were obtained from the largest health care institution in Taiwan, the Chang Gung Memorial Hospital (CGMH), which receives 10–12% of the National Health Insurance budget according to government statistics. The Chang Gung Research Database (CGRD) was used. This database combines original medical records from four medical institutes (Keelung, Linkou, Chiayi, and Kaohsiung branches) located from northern to southern Taiwan.

**Patients**

All patients who experienced paraquat poisoning, visited the emergency department (ED), and had confirmed paraquat intoxication (i.e., urine paraquat concentration ≥ 5 ppm) from January 2004 to December 2016 were included in the study. Patients who were transferred to other hospitals, discharged against medical advice (DAMA), or exhibited marked hypoxia (SpO2 < 90%) at initial presentation were excluded.
**Measurements**

Liberal oxygen therapy was defined as patients receiving oxygen therapy (supplied by a nasal cannula or mask) before marked hypoxia developed (defined as \( \text{SpO}_2 \geq 90\% \)). Conservative oxygen therapy was defined as patients receiving oxygen therapy only if marked hypoxia occurred (defined as \( \text{SpO}_2 < 90\% \)). In-hospital mortality and impending death discharge were viewed as mortality [28–30]. The following patient demographics were extracted from the CGRD: age, sex, vital signs, blood creatinine level, urine and blood paraquat concentration (ppm), cyclophosphamide treatment, hemoperfusion, intubation, and signed Do Not Resuscitate (DNR). The paraquat concentration is semi-quantitatively analyzed and the upper limit of this analysis is 50 ppm in urine and 10 ppm in blood.

**Data analysis**

For continuous variables with normal distribution: age was summarized as mean ± standard deviation. For continuous variables with non-normal distribution: vital signs, paraquat concentrations, and blood creatinine levels were expressed as medians and first quartiles to third quartiles (Q1-Q3). The distributions of categorical data were presented as numbers and percentages. Student’s t-test and the Mann-Whitney U test were used to analyze continuous variables with normal and non-normal distributions, respectively. The chi-square test was used to analyze categorical data. To determine the odds ratios between the variables and mortality, we carried out a multivariate logistic regression. Variables with a \( P \)-value <0.2 in the univariate analysis between the survival and mortality groups were included in the logistic regression analysis. The effects were estimated in terms of adjusted odds ratios (aORs) with the corresponding 95% confidence intervals (CIs). Results were considered statistically significant for a 2-tailed test if \( P < 0.05 \). All statistical analyses were performed using SPSS for Windows, version 22.0 (released 2013, IBM Corp., Armonk, NY).

**Results**

Fig 1 shows the flowchart of enrollment and the status of patients with PQ poisoning. After excluding patients who were non-critical and DAMA, transferred to other hospitals, or exhibited marked hypoxia at initial presentation, a total of 416 patients were enrolled. The baseline clinical characteristics of patients with PQ poisoning are shown in Table 1. Of the 416 patients who suffered from PQ poisoning, 334 received conservative oxygen therapy and 82 received liberal oxygen therapy. Higher intubation and overall mortality rates were observed in patients who received liberal oxygen therapy. Higher intubation and overall mortality rates were observed in patients who received liberal oxygen therapy \( (P = 0.001 \text{ and } P = 0.007, \text{ respectively}) \).

A comparison between the survival group and mortality group (Table 2) showed that the survival group exhibited a younger age \((42 \pm 14.7 \text{ vs. } 54 \pm 17.1 \text{ years, } P < 0.001)\) and lower blood paraquat concentration \((0.5 \text{ [0.1–2] \text{ vs. } 10 \text{ [4.5–10] ppm, } P < 0.001})\). The respiratory rate during triage, blood creatinine level, rates of intubation, patients with DNR status, and liberal oxygen therapy administration were also higher in the mortality group.

After analysis with binary logistic regression, the age, blood creatinine, blood paraquat concentration, patients with DNR status, and liberal oxygen therapy were all associated with mortality (Table 3). Fewer patients received cyclophosphamide treatment in the mortality group, but there was no association between cyclophosphamide treatment and mortality (aOR: 1.04, 95% CI: 0.437–2.490).

The adjusted odds ratios and 95% confidence intervals of age, blood paraquat concentration, intubation, and liberal oxygen therapy between different times of mortality are shown in Fig 2. Older age and higher blood paraquat concentrations were associated with higher
A retrospective database review between January 2004 and December 2016, total 533 patients experienced paraquat poisoning with urine paraquat concentration ≥ 5 ppm.

Patients were enrolled in this study.
(N=416)

There were 117 patients been excluded, 5 escaped at emergency department (ED), 44 were non-critical DAMA at ED, 21 were non-critical DAMA after admission, 8 transferred to other hospital, and 39 were marked hypoxia (SpO2<90%) initially.

Patients who received oxygen therapy before marked hypoxia (SpO2 ≥ 90%) were defined as receiving liberal oxygen therapy.
Patients who did not receive oxygen therapy until marked hypoxia (SpO2 < 90%) developed were defined as receiving conservative oxygen therapy.

Patients received conservative oxygen therapy. (n= 334)

Survival (n=88)
Mortality (n=246)

Patients received liberal oxygen therapy. (n= 82)

Survival (n=10)
Mortality (n=72)

Fig 1. Flowchart of enrollment and the status of patients upon enrollment.
https://doi.org/10.1371/journal.pone.0245363.g001
### Table 1. Clinical characteristics of patients with paraquat poisoning who received conservative and liberal oxygen therapy (N = 416).

|                        | Conservative oxygen therapy n = 334 | Liberal oxygen therapy n = 82 | p-value |
|------------------------|-------------------------------------|-------------------------------|---------|
| Age                    | 51 ± 17.1                           | 55 ± 18.3                     | 0.050   |
| Male sex               | 244 (73.1)                          | 51 (62.2)                     | 0.052   |
| Current smoker         | 200 (59.9)                          | 70 (85.4)                     | <0.001  |
| Chronic lower respiratory diseases | 2 (0.6)                | 4 (4.9)                       | 0.015   |
| Malignant neoplasms of lung | 0 (0.0)                | 1 (1.2)                       | 0.197   |
| Body temperature during triage (˚C) | 36.1 (35.6–36.7) | 36.0 (35.3–36.6) | 0.181   |
| Heart rate during triage | 92 (79–106.5)                      | 92.5 (78–107)                 | 0.948   |
| Respiratory rate during triage | 20 (18–20)                         | 20 (18–22)                    | 0.359   |
| Mean arterial pressure during triage | 103.3 (89.7–118.0)   | 105.8 (93.3–121.0)            | 0.390   |
| SpO2 during triage (%)  | 98 (95–100)                         | 98 (95–100)                   | 0.351   |
| Glasgow Coma Scale (GCS) | 15 (13–15)                         | 15 (11–15)                    | 0.624   |
| Urine paraquat concentration (ppm) | 50 (50–50)                        | 50 (50–50)                    | 0.462   |
| Blood paraquat concentration (ppm) | 8.5 (1.5–10)                  | 8.6 (1.1–10)                  | 0.950   |
| Blood creatinine level (mg/dL) | 1.8 (1.1–2.8)                    | 1.7 (1.3–3.6)                 | 0.252   |
| Hemoperfusion           | 236 (70.7)                         | 58 (70.7)                     | 0.990   |
| Intubation              | 42 (12.6)                          | 23 (28)                       | 0.001   |
| Signed Do Not Resuscitate (DNR) | 172 (51.5)                       | 49 (59.8)                     | 0.179   |
| Mortality               |                                     |                               |         |
| 3-day mortality         | 191 (57.2)                         | 46 (56.1)                     | 0.858   |
| 7-day mortality         | 217 (65)                           | 59 (72)                       | 0.231   |
| 28-day mortality        | 239 (71.6)                         | 69 (84.1)                     | 0.020   |
| Overall mortality       | 246 (73.7)                         | 72 (87.8)                     | 0.007   |

Data are presented as number (percentage), mean ± SD, or median (Q1-Q3).

Abbreviations: SpO2, peripheral oxygen saturation.

https://doi.org/10.1371/journal.pone.0245363.t001

### Table 2. Clinical characteristics of patients between survival and overall mortality patients (N = 416).

|                        | Survival patients n = 98 | Mortality patients n = 318 | p-value |
|------------------------|--------------------------|-----------------------------|---------|
| Age                    | 42 ± 14.7                | 54 ± 17.1                   | <0.001  |
| Male sex               | 64 (65.3)                | 231 (72.6)                  | 0.162   |
| Body temperature during triage (˚C) | 36.5 (36.0–36.9)      | 36.0 (35.4–36.5)            | <0.001  |
| Heart rate during triage | 91 (79–102)               | 92 (79–108)                 | 0.343   |
| Respiratory rate during triage | 19 (18–20)              | 20 (18–22)                  | 0.001   |
| Mean arterial pressure during triage | 103.3 (92.3–116.0)     | 104.2 (89.7–119.0)          | 0.966   |
| Glasgow Coma Scale (GCS) | 15 (15–15)               | 15 (10–15)                  | <0.001  |
| Blood paraquat concentration (ppm) | 0.5 (0.1–2)             | 10 (4.5–10)                 | <0.001  |
| Blood creatinine level (mg/dL) | 0.9 (0.7–1.4)           | 2 (1.4–3.1)                 | <0.001  |
| Hemoperfusion           | 74 (75.5)                | 220 (69.2)                  | 0.229   |
| Intubation              | 4 (4.1)                  | 61 (19.2)                   | <0.001  |
| Signed Do Not Resuscitate (DNR) | 14 (14.3)               | 207 (65.1)                  | <0.001  |
| Liberal oxygen therapy  | 10 (10.2)                | 72 (22.6)                   | 0.007   |

Data are presented as number (percentage), mean ± SD, or median (Q1-Q3).

https://doi.org/10.1371/journal.pone.0245363.t002
mortality rates. Liberal oxygen therapy was associated with a higher 28-day mortality rate (aOR, 4.71; 95% CI, 1.533–14.471) and a higher overall mortality rate (aOR: 5.97, 95% CI: 1.692–21.049).

The model was adjusted for age, male sex, smoking status (current smoker or not), chronic lower respiratory diseases, malignant neoplasms of the lung, body temperature during triage, respiratory rate during triage, Glasgow Coma Scale, blood paraquat concentration (ppm), blood creatinine level (mg/dL), cyclophosphamide treatment, intubation, signed Do Not Resuscitate, and liberal oxygen therapy.

In the subgroup analysis, among the 55 intubated patients with their inspired oxygen fraction (FiO2) recorded after intubation, 26 and 29 used high FiO2 (≥40%) and low FiO2 (<40%) when starting the mechanical ventilator, respectively. The mortality rate was 96.1% and 89.6% in the high and low FiO2 group, respectively (P = 0.613). There were 17 patients who initially received high FiO2 in the conservative group (n = 36), and 9 patients initially received high FiO2 in the liberal group (n = 19) (47.2% and 47.4% in the conservative and liberal groups, respectively, P = 0.992). There were 10 patients who did not have FiO2 records after intubation due to mortality soon after intubation.

Discussion

This study involved 416 patients who experienced paraquat intoxication between January 2004 and December 2016 (Fig 1). Mortality rates were 87.8% and 73.7% in the liberal and conservative oxygen therapy groups, respectively (Table 1). Global mortality rates associated with paraquat intoxication have been reported to range from 8% to 78.6% in previous studies [30–32]. The mortality rate was higher in Taiwan (approximately 60%–90%) [33, 34], which could be a result of the accessibility of paraquat, which was not banned in Taiwan until February 2019 [35, 36].

Patients who survived paraquat poisoning were younger (42 ± 14.7 and 54 ± 17.1 years, in the survival and mortality groups, respectively, P < 0.001) and exhibited lower blood paraquat concentration (0.5 [0.1–2] vs. 10 [4.5–10] ppm in the survival and mortality groups,
respectively, $P < 0.001$) (Table 2). In previous studies, the mortality rate of paraquat intoxication was closely related to age and blood paraquat concentration [30, 37]. The association between mortality and older age, and mortality and higher blood PQ levels were still observed after further analysis of the data with binary logistic regression. Similar to previous studies
[38–41], older ages and higher blood paraquat levels were associated with almost all mortality periods in this study (Fig 2A and 2B).

Mortality was also associated with blood creatinine levels, patients with DNR status, and liberal oxygen therapy (Table 3). Paraquat is primarily eliminated unchanged by the renal system through glomerular filtration and active tubular secretion [42]. It causes acute tubular necrosis, hypoperfusion from hypovolemia/hypotension, and direct glomerular injury following poisoning, which may lead to the development of acute kidney injury [43]. Over 90% of paraquat is excreted in the urine within the first 24 h of poisoning if the renal function is normal [17]. Renal impairment prolongs the elimination of paraquat, which contributes to mortality.

Patients who were intubated due to respiratory failure were associated with a higher overall mortality rate (aOR: 4.30, 95% CI: 1.07–17.303), but were not associated with mortality before 28 days (Fig 2C). In the subgroup analysis among intubated patients, there were 55 patients who had recorded FiO2 levels. The rates of using high FiO2 at the initial phase were not statistically significant between the conservative and liberal groups (47.2% and 47.4%, respectively, \( P = 0.992 \)). The mortality rate was higher in the high FiO2 group (96.1% and 89.6% in the high and low FiO2 groups, respectively, \( P = 0.613 \)), but the difference was not statistically significant. This finding was similar to that of previous studies [3, 44] and might be explained by the different stages of lung injuries caused by paraquat. The initial toxicological effects of paraquat on the lungs are destruction of the alveolar type I and type II epithelial cells, which occur within 1–3 days of poisoning [41, 45–47]. Damage to type I alveolar cells impairs gas exchange between the air space and the capillaries, which compromises lung function from the beginning of paraquat intoxication. The main functions of type II cells are surfactant secretion, active transport of water and ions, and epithelial regeneration. Destruction of type II cells results in increased surface tension within the alveoli, which draws fluid from capillaries to produce edema [48]. The influx of inflammatory cells, mainly neutrophils, macrophages, and eosinophils to the interstitial and alveolar spaces takes place during this destructive phase and is maintained throughout the proliferative phase. Because of this, alveolitis, pulmonary edema, acute pneumonitis, and hemorrhage develop. The proliferative phase, the second phase of paraquat-induced lung toxicity, occurs several days after paraquat ingestion and results in the development of extensive pulmonary fibrosis. The effectiveness of gas exchange is then reduced, which leads to death as a consequence of severe, refractory hypoxia.

As shown in Fig 2D, 28-day mortality and overall mortality (aOR, 4.71; 95% CI, 1.53–14.47; aOR, 5.97; 95% CI, 1.69–21.049, respectively) were associated with liberal oxygen therapy. This may be related to the production of cytotoxic reactive oxygen species. Superoxide radicals are formed by paraquat redox cycling and are susceptible to further reactions by other intracellular processes, leading to the formation of other reactive oxygen species that are also potentially cytotoxic. Paraquat redox cycling continues if nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen are available. Depletion of NADPH prevents the recycling of glutathione and exacerbates toxicity by interfering with other intracellular processes such as energy production and active transport. Intracellular protective mechanisms such as superoxide dismutase and glutathione are also depleted, which further impairs the intracellular clearance of reactive oxygen species. Oxygen supply is believed to amplify the formation of reactive oxygen species. Previous studies also demonstrated that oxygen supply leads to type II pneumocyte injury and impaired pulmonary function [24, 45]. The contribution of liberal oxygen therapy to mortality was more prominent than intubation (aOR = 5.97, \( P = 0.005 \) and 4.30, \( P = 0.04 \), respectively, separately shown in Table 3). This might imply that oxygen supply may worsen pulmonary functions and architecture by promoting the process of cytotoxic reactions. Therefore, clinicians should closely monitor oxygen saturation and respiration patterns.
in patients with PQ poisoning. Oxygen therapy should be administered with caution and should be reserved for those with hypoxia (SpO2 < 90%).

**Limitations**

This study has some limitations. First, we excluded patients who were transferred to other hospitals, escaped or were DAMA. This might have resulted in the higher mortality rates observed in this study. Second, due to the retrospective nature of the study, selection bias cannot be ignored. Patients might have looked much sicker (e.g., shallow breathing or breathing with accessory muscle use), and received “liberal oxygen” even if their oxygen saturation was above 90%. Thus, they ended up having worse conditions. Finally, the limitations of the retrospective design might have introduced some confounding factors that could have altered the values of oxygen saturation. For example, oximeter readings could be influenced by cold extremities or oxygen therapy may be applied by the emergency medical technicians (EMT) outside the hospital.

**Conclusions**

Unless the evidence of hypoxia (SpO2 < 90%) is clear, oxygen therapy should be avoided because it is associated with increased mortality.

**Supporting information**

S1 Data.

(XLSX)

**Acknowledgments**

The authors would like to thank the Taiwanese Government for banning paraquat in February 2019 and acknowledge all clinical physicians for their struggle and effort to manage patients with PQ poisoning. The corresponding author Po-Chun Chuang thanks Doctor Ja-Liang Lin who contributed his life to toxicology and medical education in Taiwan.

**Author Contributions**

**Conceptualization:** Chao-Jui Li, Po-Chun Chuang.

**Data curation:** Fu-Jen Cheng, Po-Chun Chuang.

**Methodology:** Po-Chun Chuang.

**Supervision:** Hsiu-Yung Pan, Fu-Jen Cheng, Kuo-Chen Huang, Chao-Jui Li, Chien-Chih Chen, Po-Chun Chuang.

**Visualization:** Chien-Chih Chen.

**Writing – original draft:** Xin-Hong Lin.

**Writing – review & editing:** Xin-Hong Lin, Hsiu-Yung Pan.

**References**

1. Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: systematic review. BMC Public Health. 2007; 7:357. https://doi.org/10.1186/1471-2458-7-357 PMID: 18154668
2. Bertolote JM, Fleischmann A, Butchart A, Besbelli N. Suicide, suicide attempts and pesticides: a major hidden public health problem. Bull World Health Organ. 2006; 84(4):260. https://doi.org/10.2471/blt.06.030668 PMID: 16628293

3. Wu MR, Hsiao CY, Cheng CH, Liao FC, Chao CL, Chen CY, et al. Is endotracheal intubation a non-beneficial treatment in patients with respiratory failure due to paraquat poisoning? PLoS One. 2018; 13(3): e0195071. https://doi.org/10.1371/journal.pone.0195071 PMID: 29590187

4. Li K, Cheng X, Jiang J, Wang J, Xie J, Hu X, et al. The toxic influence of paraquat on hippocampal neurogenesis in adult mice. Food Chem Toxicol. 2017; 106(Pt A):356–66. https://doi.org/10.1016/j.fct.2017.05.067 PMID: 28576469

5. Dodge AD. The mode of action of the bipyridylum herbicides, paraquat and diquat. Endeavour. 1971; 30(111):130–5. https://doi.org/10.1016/0160-9327(71)90039-1 PMID: 4110469

6. Suntres ZE. Role of antioxidants in paraquat toxicity. Toxicology. 2002; 180(1):65–77. https://doi.org/10.1016/s0300-483x(02)00382-7 PMID: 12324200

7. Kelner MJ, Bagnell R. Paraquat resistance associated with reduced NADPH reductase in an energy-dependent paraquat-accumulating cell line. Arch Biochem Biophys. 1989; 274(2):366–74. https://doi.org/10.1016/0003-9861(89)90450-5 PMID: 2802616

8. Bus JS, Gibson JE. Paraquat: model for oxidant-initiated toxicity. Environ Health Perspect. 1984; 55:37–46. https://doi.org/10.1289/ehp.845537 PMID: 6329674

9. Saeed SA, Wilks MF, Coupe M. Acute diquat poisoning with intracerebral bleeding. Postgrad Med J. 2001; 77(907):329–32. https://doi.org/10.1136/pgmj.77.907.329 PMID: 11320278

10. Yang W, Tiffany-Castiglioni E. The bipyridyl herbicide paraquat induces proteasome dysfunction in human neuroblastoma SH-SY5Y cells. J Toxicol Environ Health A. 2007; 70(21):1849–57. https://doi.org/10.1080/15287390701459262 PMID: 17934957

11. Castello PR, Drechsel DA, Patel M. Mitochondria are a major source of paraquat-induced reactive oxygen species production in the brain. J Biol Chem. 2007; 282(19):14186–93. https://doi.org/10.1074/jbc.M700827200 PMID: 17389593

12. Bonneh-Barkay D, Reaney SH, Langston WJ, Di Monte DA. Redox cycling of the herbicide paraquat in microglial cultures. Brain Res Mol Brain Res. 2005; 134(1):52–6. https://doi.org/10.1016/j.molbrainres.2004.11.005 PMID: 15790529

13. Adam A, Smith LL, Cohen GM. An assessment of the role of redox cycling in mediating the toxicity of paraquat and nitrofurantoin. Environ Health Perspect. 1990; 85:113–7. https://doi.org/10.1289/ehp.85-1568326 PMID: 2384057

14. Bus JS, Aust SD, Gibson JE. Paraquat toxicity: proposed mechanism of action involving lipid peroxidation. Environ Health Perspect. 1976; 16:139–46. https://doi.org/10.1289/ehp.7616139 PMID: 1017417

15. Yasaka T, Ohya I, Matsumoto J, Shiramizu T, Sasaguri Y. Acceleration of lipid peroxidation in human paraquat poisoning. Arch Intern Med. 1981; 141(9):1169–71. PMID: 7259376

16. Keeling PL, Smith LL. Relevance of NADPH depletion and mixed disulfide formation in rat lung to the mechanism of cell damage following paraquat administration. Biochem Pharmacol. 1982; 31(20):3243–9. https://doi.org/10.1016/0006-2952(82)90557-3 PMID: 7150352

17. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011; 72(5):745–57. https://doi.org/10.1111/j.1365-2125.2011.04268.x PMID: 21615775

18. Tawara T, Fukushima T, Hojo N, Isobe A, Shiwaku K, Setogawa T, et al. Effects of paraquat on mitochondrial electron transport system and catecholamine contents in rat brain. Arch Toxicol. 1996; 70(9):585–9. https://doi.org/10.1007/s002040050316 PMID: 8831909

19. Rio MJ, Velez-Pardo C. Paraquat induces apoptosis in human lymphocytes: protective and rescue effects of glucose, cannabinoids and insulin-like growth factor-1. Growth Factors. 2008; 26(1):49–60. https://doi.org/10.1080/08977190801984205 PMID: 18365879

20. Denicola A, Raddi R. Peroxynitrite and drug-dependent toxicity. Toxicology. 2005; 208(2):273–88. https://doi.org/10.1016/j.tox.2004.11.023 PMID: 15615191

21. Cappelletti G, Maggioni MG, Maci R. Apoptosis in human lung epithelial cells: triggering by paraquat and modulation by antioxidants. Cell Biol Int. 1998; 22(9–10):671–8. https://doi.org/10.1006/cbir.1998.0305 PMID: 10452837

22. Smith P, Heath D. Paraquat. CRC Crit Rev Toxicol. 1976; 4(4):411–45. https://doi.org/10.1080/1040847609164020 PMID: 791582

23. Sevitt S. Diffuse and focal oxygen pneumonitis. A preliminary report on the threshold of pulmonary oxygen toxicity in man. J Clin Pathol. 1974; 27(1):21–30. https://doi.org/10.1136/jcp.27.1.21 PMID: 4406279
24. Pratt IS, Keeling PL, Smith LL. The effect of high concentrations of oxygen on paraquat and diquat toxicity in rats. Arch Toxicol Suppl. 1980; 4:415–8. https://doi.org/10.1007/978-3-642-67729-8_95 PMID: 6933951

25. Hoet PH, Demedics M, Nemery B. Effects of oxygen pressure and medium volume on the toxicity of paraquat in rat and human type II pneumocytes. Hum Exp Toxicol. 1997; 16(6):305–10. https://doi.org/10.1177/096037279701600602 PMID: 9219025

26. Gawarammana I, Buckely NA, Mohamed F, Naser K, Jeganathan K, Ariyannanada PL, et al. High-dose immunosuppression to prevent death after paraquat self-poisoning—a randomised controlled trial. Clin Toxicol (Phila). 2018; 56(7):633–9. https://doi.org/10.1080/15563650.2017.1394465 PMID: 29098875

27. Yeh YT, Chen CK, Lin CC, Chang CM, Lan KP, How CK, et al. Does Hemoperfusion Increase Survival in Acute Paraquat Poisoning? A Retrospective Multicenter Study. Toxics. 2020; 8(4). https://doi.org/10.3390/toxics8040084 PMID: 33050540

28. Lin HY, Kang SC, Chen YC, Chang YC, Wang WS, Lo SS. Place of death for hospice-care terminal patients with cancer: A nationwide retrospective study in Taiwan. J Chin Med Assoc. 2017; 80(4):227–32. https://doi.org/10.1016/j.jcma.2016.10.009 PMID: 28169209

29. Nagata I, Abe T, Uchida M, Saitoh D, Tamiya N. Ten-year inhospital mortality trends for patients with trauma in Japan: a multicentre observational study. BMJ Open. 2018; 8(2):e016635. https://doi.org/10.1136/bmjopen-2017-018635 PMID: 29439071

30. Weng CH, Hu CC, Lin JL, Lin-Tan DT, Huang WH, Hsu CW, et al. Sequential organ failure assessment score can predict mortality in patients with paraquat intoxication. PLoS One. 2012; 7(12):e51743. https://doi.org/10.1371/journal.pone.0051743 PMID: 23272154

31. Zyoud SH. Investigating global trends in paraquat intoxication research from 1962 to 2015 using bibliometric analysis. Am J Ind Med. 2018; 61(6):462–70. https://doi.org/10.1002/ajim.22835 PMID: 29537078

32. Oghabian Z, Williams J, Mohajeri M, Nakhae S, Shojaeepour S, Amirabadizadeh A, et al. Clinical Features, Treatment, Prognosis, and Mortality in Paraquat Poisonings: A Hospital-Based Study in Iran. J Res Pharm Pract. 2019; 8(3):129–36. https://doi.org/10.4103/jrpp.JRPP_18_71 PMID: 31728343

33. Hsu CW, Lin JL, Lin-Tan DT, Chen KH, Yen TH, Wu MS, et al. Early hemoperfusion may improve survival of severely paraquat-poisoned patients. PLoS One. 2012; 7(10):e48397. https://doi.org/10.1371/journal.pone.0048397 PMID: 23127593

34. Ko DR, Chung SP, You JS, Cho S, Park Y, Chun B, et al. Effects of Paraquat Ban on Herbicide Poisoning-Related Mortality. Yonsei Med J. 2017; 58(4):859–66. https://doi.org/10.3349/ymj.2017.58.4.859 PMID: 28541002

35. Chang S-S, Gunnell DJ, JoP. Banning paraquat would prevent nearly 200 deaths from suicide per year in Taiwan. 2019; 33(3):119.

36. Lee Y, Lee JH, Seong AJ, Hong CK, Lee HJ, Shin DH, et al. Arterial lactate as a predictor of mortality in emergency department patients with paraquat poisoning. Clin Toxicol (Phila). 2012; 50(1):52–6. https://doi.org/10.3109/15563650.2011.639716 PMID: 22175790

37. Zhou CY, Kang X, Li CB, Li XH, Liu Y, Wang Z, et al. Pneumomediastinum predicts early mortality in acute paraquat poisoning. Clin Toxicol (Phila). 2015; 53(6):551–6.

38. Kang C, Kim SC, Lee SH, Jeong JH, Kim DS, Kim DH. Absolute lymphocyte count as a predictor of mortality in emergency department patients with paraquat poisoning. PLoS One. 2013; 8(10):e78160. https://doi.org/10.1371/journal.pone.0078160 PMID: 24205140

39. Chan BS, Lazzaro VA, Seale JP, Duggin GG. The renal excretory mechanisms and the role of organic cations in modulating the renal handling of paraquat. Pharmacol Ther. 1998; 79(3):193–203. https://doi.org/10.1016/s0163-7258(98)00015-1 PMID: 9776376

40. Weng CH, Chen HH, Hu CC, Huang WH, Hsu CW, Fu JF, et al. Predictors of acute kidney injury after paraquat intoxication. Oncotarget. 2017; 8(31):51345–54. https://doi.org/10.18632/oncotarget.17975 PMID: 28881652
44. Khazraei S, Marashi SM, Sanaei-Zadeh H. Ventilator settings and outcome of respiratory failure in paraquat-induced pulmonary injury. Sci Rep. 2019; 9(1):16541. https://doi.org/10.1038/s41598-019-52939-3 PMID: 31719587

45. Kehrer JP, Haschek WM, Witschi H. The influence of hyperoxia on the acute toxicity of paraquat and diquat. Drug Chem Toxicol. 1979; 2(4):397–408. https://doi.org/10.3109/01480547909016033 PMID: 540539

46. Dinis-Oliveira RJ, Duarte JA, Sanchez-Navarro A, Remiao F, Bastos ML, Carvalho F. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol. 2008; 38(1):13–71. https://doi.org/10.1080/10408440701669959 PMID: 18161502

47. Khosya S, Gothwal S. Two cases of paraquat poisoning from kota, rajasthan, India. Case Rep Crit Care. 2012; 2012:652146. https://doi.org/10.1155/2012/652146 PMID: 24826339

48. Gardiner AJ. Pulmonary oedema in paraquat poisoning. Thorax. 1972; 27(1):132–5. https://doi.org/10.1136/thx.27.1.132 PMID: 5017564