



## Original Article

## Palliative Care on Patients With Paraquat Poisoning: Analysis of 90 Cases From 2005–2016



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## ARTICLE INFO

## Article history:

Received 20 June 2017

Received in revised form

16 January 2018

Accepted 9 February 2018

Available online 2 March 2018

## Keywords:

paraquat,  
palliative care,  
do-not-resuscitate,  
respiratory failure

## SUMMARY

**Background:** Paraquat poisoning has high mortality rate. Hospice services have been provided by National Health Insurance program in Taiwan since 2000, and were expanded to noncancer illnesses in September 2009. The palliative care strategy and the impact of this expanded palliative care policy on patients with paraquat poisoning remain unclear.

**Methods:** The study included 90 in-patients with paraquat poisoning, hospitalized between January 2005 and April 2016. We analyzed these patients by two factors, survivors vs. non-survivors and patients admitted between 2005 and 2010 vs. between 2011 and 2016, to compare the differences in life-sustaining treatment orders, symptom management, and use of non-beneficial life-sustaining treatments.

**Results:** The mortality rate was 75.6% and patients progressed rapidly to death (mean time: 74.69 h). 91.2% of non-survivors had a do-not-resuscitate order. Within the 24 h before death, non-survivors in the 2011–2016 group had significantly less treatment with vasopressors ( $p < 0.001$ ) and mechanical ventilation ( $p = 0.004$ ), and cardiopulmonary resuscitation ( $p = 0.008$ ) than those in the 2005–2010 group. There was no difference in use of antibiotics, immunosuppressive agents, hemoperfusion, and opioids or benzodiazepines.

**Conclusion:** Patients with paraquat poisoning are suitable candidates to have palliative care, owing to the extremely high mortality rate and rapid disease progression. The expanded palliative care policy had a positive impact on terminal paraquat poisoning patients; it decreased non-beneficial life-sustaining treatments in the end-stage of disease. Nevertheless, there is still much room for improvement in our management of paraquat poisoning by reducing non-beneficial life-sustaining treatments and reinforcing palliative treatments.

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## 1. Introduction

Paraquat is one of the major herbicides used in the agricultural countryside of Taiwan, and it can be ingested accidentally or during a suicide attempt.<sup>1</sup> In fact, paraquat poisoning accounts for two-thirds of the herbicide suicides in Taiwan.<sup>2</sup> The high toxicity of

paraquat results in extremely high mortality.<sup>3</sup> In current practice, the therapeutic regimen mainly consists of immunosuppressive agents, cyclophosphamide (CP), and methylprednisolone (MP). The use of CP and MP pulse therapy comes from the experience of treating patients with severe lung injury secondary to systemic lupus erythematosus,<sup>4,5</sup> since lung injury is also the primary cause of mortality in paraquat poisoning.<sup>6</sup> Activated charcoal hemoperfusion is also used to decrease the concentration of paraquat in plasma.<sup>7,8</sup> Traditionally in Taiwan, any aggressive treatment to maintain the patient's vital signs were used, and the quality of life of the patients were often neglected. In spite of the aggressive disease management, the mortality of paraquat poisoning is still

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high. From the data analyzed by Wu et al. between 1997 and 2009, the mortality rate was 78.6% for the 1811 patients hospitalized for paraquat poisoning in Taiwan.<sup>9</sup>

The central principle of palliative care, as defined by the World Health Organization, is to prevent and relieve suffering by “early” identification, assessment, and treatment of pain and other types of physical, psychological, emotional, and spiritual distress.<sup>10</sup> Thus, terminal patients with paraquat poisoning can also be candidates for palliative care. Hospice services have been provided by the National Health Insurance program in Taiwan since 2000, and were expanded to noncancer illnesses in September 2009. The expanded hospice services to noncancer illness include the diagnosis of organic psychotic conditions, brain deterioration, heart failure, chronic obstructive pulmonary disease, other diseases of the lung (such as severe fibrotic lung disease), liver cirrhosis, and acute or chronic renal failure in the funding program. The expanded policy is a landmark shift and has positively impacted noncancer hospice care in Taiwan.<sup>11</sup> The impact of this expanded palliative care policy on patients with paraquat poisoning remains unclear. Therefore, we conducted a study on the medical treatment of paraquat poisoning, comparing patients before and after this expanded palliative care policy.

## 2. Materials and methods

### 2.1. Subjects

This retrospective observational study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Mackay Memorial Hospital, with IRB number 15MMHIS072. The patient records and information were anonymized and de-identified prior to analysis. Patients with paraquat poisoning admitted in Taitung Mackay Memorial Hospital between January 2005 and April 2016 were included in this study, and Taitung Mackay Memorial Hospital is a regional teaching hospital in eastern Taiwan providing 500 beds and 24 h accident and emergency service. Patients who had age <20 years old or unavailability of follow-up data were excluded from the study. 90 consecutive patients with paraquat ingestion were admitted to the Taitung Mackay Memorial Hospital. Of the 90 patients, 22 survived and 68 died. Medical history, clinical signs, and laboratory examinations were used to diagnose paraquat poisoning. Without a spectrophotometer to measure plasma paraquat concentration, a qualitative urine-sodium dithionite reaction was used. Demographic data, do-not-resuscitate (DNR) orders, prescribed medications, length of stay, and intra-hospital course were obtained from the hospital medical registry.

### 2.2. Before and after the expanded policy regarding noncancer illness

The patients are categorized by their admission date. We chose 2010/2011 as the division point because we theorized that the expanded policy regarding terminal noncancer conditions may take time to influence physicians' clinical practice. We also show the treatment administered to patients within the 24 h before the death. This included the continuous use of antibiotics, immunosuppressive agents, hemoperfusion, and the administration of opioids or benzodiazepines.

### 2.3. Definition of do-not-resuscitate and do-not-intubate orders

DNR orders instruct medical staff not to administer cardiopulmonary resuscitation when a patient progresses to cardiac

arrest. The procedures of resuscitation include cardiac massage, airway management with endotracheal intubation, epinephrine/vasopressin injection, or even defibrillation if the electrocardiogram shows ventricular arrhythmia. Beyond resuscitation attempts, the patients with DNR orders can still receive varieties of aggressive disease management in clinical practice, such as immunosuppressive therapy and hemoperfusion. In general, a do-not-intubate (DNI) order is in effect immediately after patients sign the DNR consent form. However, some patients receive DNR orders after they have already been intubated. In these situations, the DNR orders are consented by their surrogate decision-makers (e.g., family members and legal guardians) because of the impaired communication ability with an endotracheal tube.<sup>12</sup>

### 2.4. Statistical analysis

Results are expressed as the mean ± standard deviation or as percentages. Student's *t*-test was used to compare differences between groups for continuous variables, and the chi-square test was employed for categorical data. A *p*-value <0.05 was considered significant. All statistical analyses were performed using the SPSS software, version 22 (IBM SPSS Statistics, Armonk, NY).

## 3. Results

### 3.1. Survivors vs. non-survivors

The mean age of the 90 patients with paraquat poisoning was 55.16 ± 17.44 years, and 56 patients (62.2%) were men. As seen in Table 1, the overall mortality rate for the entire population was 75.6% (68 of 90 patients). Non-survivors were significantly older (57.72 ± 17.42 years vs. 47.23 ± 15.27 years, *p* = 0.01), received more DNR orders (91.2% or 62 of 68 patients vs. 18.2% or 4 of 22 patients, *p* < 0.001), received more endotracheal intubation for respiratory failure (47.1% or 32 of 68 patients vs. 0% or 0 of 22 patients, *p* < 0.001) (Table 1). In fact, all non-survivors experienced respiratory failure before death, significantly higher than the survivors (0 experienced respiratory failure). The percentage of patients experiencing unstable hemodynamic condition was also significantly higher in non-survivors; therefore, more of them used a vasopressor (36.8% or 25 of 68 patients vs. 0% or 0 of 22 patients, *p* < 0.001). The proportion of patients receiving pulse therapy of immunosuppressive agents, CP and MP, and hemoperfusion was insignificantly different between non-survivors and survivors.

**Table 1**  
Comparisons between survivors group and non-survivors group.

Data field	Survivors (n = 22)	Non-survivors (n = 68)	P value
Male (%)	9 (40.9)	47 (69.1)	0.02
Age (years)	47.23 ± 15.27	57.72 ± 17.42	0.01
DNR orders (%)	4 (18.2)	62 (91.2)	<0.001
CPR (%)	0 (0)	6 (8.8)	<0.001
Endotracheal Intubation (%)	0 (0)	32 (47.1)	<0.001
Respiratory failure (%)	0 (0)	68 (100)	<0.001
CP + MP pulse therapy (%)	18 (81.8)	61 (89.7)	0.14
HP (%)	22 (100)	61 (89.7)	0.29
Use of vasopressor (%)	0 (0)	25 (36.8)	<0.001
LOS in hospital (hours)	350.86 ± 186.58	74.69 ± 120.07	<0.001

DNR = do-not-resuscitate; CPR = cardiopulmonary resuscitation; CP = cyclophosphamide; MP = methylprednisolone; HP = hemoperfusion; LOS = length of stay.

### 3.2. Hospitalization between 2005 and 2010 vs. between 2011 and 2016

As seen in Table 2, there were 43 patients hospitalized with a diagnosis of paraquat poisoning between 2005 and 2010, and 47 patients between 2011 and 2016. The most notable results showed significantly more patients with DNI orders in the 2011–2016 group (55.3% or 26 of 47 patients vs. 30.2% or 13 of 43 patients,  $p = 0.02$ ), with a trend toward the increase in DNR orders over time (80.9% or 38 of 47 patients vs. 65.1% or 28 of 43 patients,  $p = 0.09$ ), but no difference in overall mortality between groups (74.5% or 35 of 47 patients vs. 76.7% or 33 of 43 patients,  $p = 0.802$ ). In the non-survivors, we compared the management in the last 24 h before death. In the 2011–2016 group of non-survivors, there was significantly less use of a vasopressor (11.4% or 4 of 35 patients vs. 54.5% or 18 of 33 patients,  $p < 0.001$ ), significantly less use of a mechanical ventilator (31.4% or 11 of 35 patients vs. 66.7% or 22 of 33 patients,  $p = 0.004$ ), and significantly less CPR administered (0% vs. 18.2% or 6 of 33 patients,  $p = 0.008$ ). There was no difference in the percentage of patients who received antibiotics, immunosuppressive agents, hemoperfusion, and opioids or benzodiazepines before the death between the 2005–2010 and 2011–2016 groups.

## 4. Discussion

Because of differences in culture and social customs, palliative care is more difficult to implement in Taiwan than in Western countries, especially in noncancer patients. When we compare cancer patients with noncancer patients, the former usually have a more predictable trajectory of disease and life expectancy.<sup>13</sup> The patient's family also shows more acceptance of palliative care for managing discomfort in terminal cancer patients. However, in fact, patients dying of a noncancer disease can experience similar symptoms to those with cancer.<sup>14</sup> The expanded hospice services in Taiwan include eight terminal noncancer conditions, which are not all chronic illnesses. Palliative care is defined as a specialized care to improve symptoms, comfort, dignity, and quality of life of patients who have a serious, life-threatening, and irreversible disease, and for the care and support of their families.<sup>15</sup> Here, we will show why we also consider patients with paraquat poisoning as candidates for palliative care.

**Table 2**

The DNR orders in all patients ( $n = 90$ ) and management on non-survivors ( $n = 68$ ) in 24 h before the death between 2005–2010 group and 2011–2016 group.

Data Field	2005–2010 ( $n = 43$ )	2011–2016 ( $n = 47$ )	P value
Male (%)	27 (62.8)	29 (61.7)	0.92
Age (years)	56.51 ± 18.17	53.92 ± 16.83	0.48
DNR orders (%)	28 (65.1)	38 (80.9)	0.09
DNI orders (%)	13 (30.2)	26 (55.3)	0.02
Death (%)	33 (76.7)	35 (74.5)	0.802
Management within 24 h before the death			
	2005–2010 ( $n = 33$ )	2011–2016 ( $n = 35$ )	
Use of antibiotic (%)	28 (84.8)	32 (91.4)	0.4
Use of vasopressor (%)	18 (54.5)	4 (11.4)	<0.001
CP + MP pulse therapy (%)	27 (81.8)	26 (74.3)	0.45
HP (%)	30 (90.9)	26 (74.3)	0.07
Mechanical ventilator (%)	22 (66.7)	11 (31.4)	0.004
CPR (%)	6 (18.2)	0 (0)	0.008
Opioids or benzodiazepines (%)	14 (42.4)	16 (45.7)	0.79

DNR = do-not-resuscitate; DNI = do-not-intubate; CP = cyclophosphamide; MP = methylprednisolone; HP = hemoperfusion; CPR = cardiopulmonary resuscitation.

Chronically ill patients may have more capacity to receive palliative care because they may have been experiencing persistent discomfort and symptoms or repetitive hospitalizations. Paraquat poisoning is an acute illness, and the patients and their family must make medical decisions in only a few hours or days. Because of legal issues, physicians in Taiwan usually need DNR consent prior to introducing full palliative care for terminally ill patients. Our results show much more DNR orders in non-survivors than in survivors (91.2% or 62 of 68 patients vs. 18.2% or 4 of 22 patients,  $p < 0.001$ ). However, there were still 32 patients in the non-survivors group who were intubated for respiratory failure before they signed DNR consent, which means nearly half of patients would not have been able to make the decisions at very first time until the symptoms progressed. We faced multiple difficulties before discussing DNR orders with patients with paraquat poisoning and their family. First, patients with paraquat poisoning may be unaware of their prognosis. Second, physicians themselves may be unaware of the criteria for eligibility of such patients to receive palliative care.<sup>16</sup> Finally, some physicians may be reluctant to discuss this issue because of their lack of skill or training in communicating with terminally ill patients.<sup>17</sup> Generally, palliative care is given to patients with a life expectancy of days or months. The overall mortality of the patients in our study was 75.6%, and the mean duration of time between admission and death in non-survivors was only 74.69 ± 120.07 h. Even survivors can experience chronic dyspnea due to residual lung fibrosis, causing restrictive type pulmonary dysfunction.<sup>18,19</sup> This makes it reasonable to consider all patients with paraquat poisoning as candidates for palliative care.

Physicians unfamiliar with paraquat toxicology may be reluctant to discuss palliative treatment. In our study, 24.4% of patients survived (22 of 90) and could benefit from aggressive treatment. We should understand that, first, physicians who certify that a patient is “likely” to be terminal status can not “guarantee” with complete certainty. Even though 22 survivors were discharged successfully, they still needed to be followed up for the sequela of pulmonary injury. Patients in hospice programs can be withdrawn if their condition unexpectedly improves, and they can also be enrolled again if the condition worsens later. Second, suitable prognostic indicators can assist physicians in identifying candidates who are likely to benefit from aggressive treatment or be harmed by inappropriate life-sustaining treatment. Plasma paraquat concentration obtained within the first 24 h is a good objective indicator,<sup>20,21</sup> but the necessary equipment is not available at Mackay Memorial Hospital. There are also some clinical indicators related to a patient's mortality. Kim et al. demonstrated that the mortality risk was significantly higher in patients with acute kidney injury.<sup>22</sup> In our study, the development of respiratory failure indeed separated survivors and non-survivors. Once it occurred, the severity of hypoxemia kept progressing, even with endotracheal intubation, ventilator support, or ongoing use of immunosuppressive agents and hemoperfusion.

DNR orders are found not only to reduce the use of cardiopulmonary support measures, but also tend to increase the use of palliative care.<sup>23,24</sup> Physicians feel more relaxed to withhold medical treatment, even though the treatment itself may little effect on the length of life. The non-survivors in the 2011–2016 group ( $n = 35$ ) did show significantly less use of mechanical ventilators and CPR before the death than those in the 2005–2010 group ( $n = 33$ ). It may be attributed to the early enactment of the Statute for Palliative Care in June 2000 and the expanded policy to non-cancer illness in September 2009. Media campaigns about the high fatality and toxicity of paraquat also have contributed to the decision of patients and their families to obtain a DNR or DNI order. However, there was no reduction in the use of some medical treatment such as antibiotics, immunosuppressive agents, and

hemoperfusion. Insufficient palliative care could have resulted in these additional medical expenditures. Furthermore, it's related to unsatisfactory control of the patient's discomfort, mainly pain and dyspnea, as the percentage of the non-survivors prescribed opioids or benzodiazepines between 2005–2010 group and 2011–2016 group was equally less than 50%. In cancer and chronic noncancer patients, there is more time to understand the prognosis and the goal of palliative care. In paraquat poisoning, however, the patients and their family usually have insufficient knowledge and mental preparation to make medical decisions.<sup>25–27</sup> Therefore, physicians should assume an educational role to initiate and proceed with palliative care when patients meet the enrollment criteria.

#### 4.1. Limitations

Our results are limited to data from a single hospital. Moreover, the retrospective nature of the study and the small patient cohort influence the certainty of our conclusions. Further studies are needed to confirm our observations.

## 5. Conclusions

Patients with paraquat poisoning are potential and suitable candidates for palliative care owing to the extremely high mortality (75.6%) of this condition and rapid progression of the disease to death (mean time: 74.69 h). A total of 91.2% of non-survivors eventually had a DNR order. The expanded palliative care policy in Taiwan has had a positive impact on patients with terminal paraquat poisoning, as it can decrease non-beneficial life-sustaining treatments in the end-stage of illness. Physicians should explain to patients and their families about the prognosis in detail and the choice of pursuing palliative care. In patients selecting palliative care, some non-beneficial life-sustaining treatments can be withheld or withdrawn, and discomfort relieving treatments should become the focus for physicians.

#### Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### Acknowledgment

We are grateful for the assistance from the nursing and medical staff of the Mackay Memorial Hospital Intensive Care Unit as their support was essential for the completion of this study.

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