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Original Article

# Survival rate after paraquat poisoning: impact of emergency clinical and laboratory variables*

## Taxa de sobrevivência após intoxicação por paraquat: impacto das variáveis clínicas emergenciais e laboratoriais

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**ABSTRACT**

**Objective:** to analyze the association of survival to emergency care measures, clinical symptoms and biochemical markers used for paraquat intoxicated patients. **Methods:** retrospective cohort, guided by the Strengthening the Reporting of Observational Studies in Epidemiology tool. The data collection and analysis protocol were based on two phases: first, with the survey of the investigation forms of exogenous poisoning from the Secretariat of Epidemiological Surveillance; second, with the analysis of information in printed medical records. **Results:** of the 36 (100%) patients investigated, 19 (53.0%) survived; regarding the clinical manifestations, there was statistical significance for the respiratory system (p=0.003); regarding the biochemical variables, there was statistical significance for liver enzymes. The initial emergency measures 13(56.5%) of survivors received gastric lavage with activated charcoal. **Conclusion:** we observed a lack of efficacy of the impacts of emergency care measures and medications in increasing patient survival.
**Descriptors:** Poisoning; Paraquat; Emergencies; Survival Rate; Amazonian Ecosystem.

**RESUMO**

**Objetivo:** analisar a associação da sobrevida às medidas de atendimento de emergência, sintomas clínicos e marcadores bioquímicos usados para pacientes intoxicados por paraquat. **Métodos:** coorte retrospectiva, norteada pela ferramenta *Strengthening the Reporting of Observational Studies in Epidemiology*. O protocolo de coleta e análise de dados foi baseado em duas fases: primeira, com o levantamento das fichas de investigação de intoxicações exógenas da Secretaria de Vigilância Epidemiológica; segunda, com a análise das informações nos prontuários médicos impressos. **Resultados:** dos 36(100%) pacientes investigados, 19(53,0%) sobreviveram; no tocante às manifestações clínicas, houve significância estatística para o sistema respiratório (p=0,003); no que tange às variáveis bioquímicas, houve significância estatística para as enzimas hepáticas. As medidas de emergências inicias 13(56,5%) dos sobreviventes receberam lavagem gástrica com carvão ativado. **Conclusão:** observou-se falta de eficácia dos impactos das medidas de atendimento de emergência e dos medicamentos em aumentar a sobrevida dos pacientes.
**Descritores:** Envenenamento; Paraquat; Emergências; Taxa de Sobrevida; Ecossistema Amazônico.

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## Introduction

Paraquat (1,1'-dimethyl-4,4'-bipyridine-dichloride) is one of the most widely used agricultural herbicides worldwide, marketed under different names and formulations, and used widely because of its low price and effectiveness, and its safety and environmental stability compared to other herbicides. The correct use of paraquat is relatively safe and is not a health hazard if the safety instructions are followed correctly. However, it is highly toxic to humans if used incorrectly or ingested orally[1].

When ingested, paraquat is absorbed in the gastrointestinal tract and distributed throughout the body via the bloodstream; ingesting 50-100ml at 20% can result in fulminant organ failure and consequently death within a few hours to a few days. However, smaller amounts may be harmful to the main target organs (kidneys and lung) and may worsen over the next 2 to 6 days with mortality rates above 50%[2]. Furthermore, the pathological effects of oxidative stress caused by intoxication include inflammation, edema, fibrosis, and necrosis of organs such as kidneys, liver, heart, and brain[3].

Thus, among the available herbicides, paraquat has the highest rate of poisonings and fatalities when ingested accidentally or intentionally. Suicide attempts are a serious problem due to the high toxicity of paraquat. Mortality rates worldwide range from 30.0 to 88.0%[3], but in suicide cases can be as high as 100.0% of cases. The main complications associated with this mortality are usually respiratory failure[4], renal failure, and multiple organ failure[5]. In addition, there is no effective antidote for paraquat poisoning and patient survival depends only on the hospital care available for treatment.

Thus, based on toxicokinetic, the most used treatments are gastric adsorbents, extracorporeal filtration, and different classes of drugs such as antioxidants, anti-inflammatory and immunosuppressants[3]. Monitoring of clinical symptoms and biochemical markers are also commonly evaluated to determine the response and need for more aggressive treatments for patients with severe paraquat poisoning[6-8]. However, the treatments used, and patient survival vary significantly between studies, and therefore the effectiveness of most of these therapeutic methods remains uncertain[2,7-8].

In Brazil, the large-scale use of herbicides is one of the factors contributing to the large number of poisoning cases, causing more than 30.0% suicide attempts. Moreover, underreporting is very common and the number of herbicide poisonings and suicide attempts throughout Brazil is much higher[9].

In this sense, everyday situations that occur at the *Complexo Hospitalar Regional de Cacoal* in the emergency and intensive care unit sectors show that poisonings are constant and constitute a relevant number of cases. Thus, the interest in building a methodological path and the urge to systematically investigate paraquat poisoning and better understand the clinical outcomes of victims emerged from the realization that little is known about the biocide action of paraquat in the human body.

In view of the exposed problematic, the following question was formulated: what is the association of survival to emergency measures, clinical manifestations and biochemical markers implemented to assist victims of paraquat poisoning?

We aimed to analyze the association of survival to emergency care measures, clinical symptoms and biochemical markers used for paraquat intoxicated patients.

## Methods

This is a retrospective cohort guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[10] tool. The study included all patients intoxicated by paraquat admitted between December 2012 and March 2018 at the *Complexo Hospitalar Estadual de Cacoal*, located in the southern

cone of Rondônia, Brazil, an Amazon region classified as the second state health region, being a reference in medium and high complexity care for a population of over 800 thousand inhabitants.

According to the study protocol, the first phase was composed of a survey of epidemiological data through the Exogenous Intoxication Notification System database of the Epidemiological Surveillance Secretariat of the municipality of Cacoal. In the second phase, information was collected from the printed medical records of 36(100%) patients with exogenous poisoning confirmed by medical diagnosis according to the International Statistical Classification of Diseases and Health Problems (ICD10), X680- Autointoxication by and intentional exposure to pesticides - residence; X489- Accidental poisoning (intoxication) from pesticide exposure - unspecified location; X689- Autointoxication from exposure, intentional, to pesticides - unspecified location; X687- Autointoxication from exposure, intentional, to pesticides - farm and X480- Accidental poisoning (intoxication) from and exposure to pesticides - residence). Information was obtained on survival, emergency care measures, biochemical variables, and clinical symptoms. Illegible, incomplete, or absent hospital records at the time of data collection, as well as records of those under 18 years of age and indigenous people were excluded. Data collection for both phases occurred in the months of May to June 2018 from Monday to Saturday over a period of 8 hours per day.

After collecting data from the first and second phases, we proceeded to analyze the association between patient survival and emergency care and of biochemical markers and clinical symptoms, and Pearson's Chi-square test and Fisher's exact test were used for categorical variables. For comparison between two numerical variables, the student t-test with equal variances, the student t-test with unequal variances, or the Mann-Whitney test were used. The margin of error used in the decision of the statistical tests was 5% for the p-value. All statistical analyses were performed in the Statistical Package for the Social Science software, version 23.

This research was approved by the Ethics and Research Committee of the Faculty of Biomedical Sciences of Cacoal with obtaining the Certificate of Presentation for Ethical Appreciation No. 70461317.7.0000.5298 and opinion No. 2,181,872/2017, it was also necessary to update the title of the research through the new opinion No. 4,530,008/2021, respecting all legal aspects of Resolution 466/12, Resolution 510/2016 of the National Health Council.

## Results

A total of 36 exogenous intoxication charts and medical records were evaluated. Of the 36(100.0%) poisoning cases, 19(53.0%) patients survived and 17(47.0%) were victims of suicide attempts and died.

In the patients who died, the primary causes were acute respiratory failure in nine (52.9%) and multiple organ failure in eight (47.1%), followed by kidney injury and cardiac arrest in seven (41.2%) respectively.

The main clinical symptoms were related to the gastrointestinal tract, such as vomiting, dysphagia, and sialorrhea, but no significant interaction with patient survival was observed. Respiratory and renal symptoms had significant interactions with patient survival, with patients with these symptoms dying around 60.0% and 75.0% respectively. In the respiratory system, dyspnea (32.5%) was the main symptom, followed by tachypnea (15%) and hypoxemia (7.5%). In the renal system, the main symptoms were anuria (15%), oliguria (15%), dysuria, and hematuria, (7.5%) respectively. There were no significant interactions between the neurological, cardiovascular, and cutaneous systems with patient survival.

**Table 1** – Influence of clinical manifestations on survival of patients intoxicated with paraquat treated at the Regional Hospital Complex. Cacoal, RO, Brazil, 2021. (n=36)

| Variables* | Deaths | Survivors | p-value |
|---|---|---|---|
| | n(%) | n(%) | |
| Neurological | | | 0.071† |
| Yes | 9(56.3) | 7(43.8) | |
| No | 3(23.1) | 10(76.9) | |
| Respiratory | | | 0.003‡ |
| Yes | 12(60.0) | 8(40.0) | |
| No | - | 9(100.0) | |
| Cardiovascular | | | 0.251‡ |
| Yes | 9(52.9) | 8(47.1) | |
| No | 3(25.0) | 9(75.0) | |
| Gastrointestinal | | | 0.622‡ |
| Yes | 9(37.5) | 15(62.5) | |
| No | 3(60.0) | 2(40.0) | |
| Renal | | | 0.006‡ |
| Yes | 9(75.0) | 3(25.0) | |
| No | 3(17.6) | 14(82.4) | |
| Cutaneous/mucosal | | | 0.071† |
| Yes | 9(56.2) | 7(43.8) | |
| No | 3(23.1) | 10(76.9) | |
| Other | | | 0.774† |
| Yes | 7(43.8) | 9(56.2) | |
| No | 5(38.5) | 8(61.5) | |

*Seven medical records were excluded from this analysis due to lack of information regarding clinical manifestations; †Fisher's exact test; ‡Chi-square test

The main biochemical markers, obtained through laboratory tests performed on the patients' blood serum were creatinine, aspartate aminotransferase and alanine aminotransferase, urea, sodium, and potassium, respectively. However, the only biochemical variables with a significant interaction with survival were aspartate aminotransferase and alanine aminotransferase. For patients who died, aspartate aminotransferase and alanine aminotransferase levels were significantly higher compared to patients who survived (144 and 71UL-1; 179 and 64UL-1 respectively).

**Table 2** – Influence of the most frequent biochemical variables on survival of patients intoxicated with paraquat and treated at the Regional Hospital Complex. Cacoal, RO, Brazil, 2021. (n=36)

| Variables* | Deaths | Survivors | p-value |
|---|---|---|---|
| | Average ± SD | Average ± SD | |
| Creatinine | 4.90 ± 2.58 | 2.72 ± 2.81 | 0.070† |
| Urea | 131.33 ± 112.60 | 65.11 ± 50.61 | 0.130† |
| Aspartate transaminase | 144.75 ± 134.97 | 71.82 ± 84.48 | 0.031† |
| Alanine transaminase | 179.63 ± 167.38 | 63.91 ± 101.18 | 0.028† |
| Potassium | 3.25 ± 0.51 | 3.43 ± 0.40 | 0.492‡ |
| Sodium | 141.38 ± 11.24 | 135.92 ± 2.76 | 0.405§ |

*Seven medical records were excluded from this analysis due to lack of information regarding biochemical tests involving intoxicated patients; †t-Student with equal variables; ‡Mann-Whitney; §t-Student with unequal variables

The emergency care measures used for the intoxicated patients were sequentially as follows; gastric lavage by nasogastric tube (57.5%), oxygen therapy (30%), indwelling urinary catheter, and hemodialysis (10%) respectively. Hemodialysis was the only emergency care measure with significance on survival, as all four (100%) patients who received this treatment did not survive.

In addition, the most used drug in the treatment of patients was acetylcysteine (47.5%), followed by ascorbic acid(45%), hydrocortisone(45%), furosemide (32.5%), methylprednisolone (20%). However, no drug used had a significant influence on patient survival.

**Table 3** – Influence of interventions in emergency care and medications on survival of patients intoxicated with paraquat and treated at the Regional Hospital Complex. Cacoal, RO, Brazil, 2021. (n=36)

| Variables | Deaths | Survivors | p-value |
|---|---|---|---|
| | n(%) | n(%) | |
| Emergency Interventions* | | | |
| Gastric lavage | | | 1.000† |
| Yes | 10(43.5) | 13(56.5) | |
| No | 3(50.0) | 3(50.0) | |
| Nasogastric tube | | | 0.219‡ |
| Yes | 6(35.3) | 11(64.7) | |
| No | 7(58.3) | 5(41.7) | |
| Oxygen therapy | | | 0.774‡ |
| Yes | 5(41.7) | 7(58.3) | |
| No | 8(47.1) | 9(52.9) | |
| Urinary catheter delay | | | 0.606† |
| Yes | 1(25.0) | 3(75.0) | |
| No | 12(48.0) | 13(52.0) | |
| Hemodialysis | | | 0.030† |
| Yes | 4(100.0) | - | |
| No | 9(36.0) | 16(64.0) | |
| Medication | | | |
| Acetylcysteine | | | 1.000‡ |
| Yes | 9(47.4) | 10(52.6) | |
| No | 4(50.0) | 4(50.0) | |
| Ascorbic acid | | | 1.000‡ |
| Yes | 9(50.0) | 9(50.0) | |
| No | 4(44.4) | 5(55.6) | |
| Hydrocortisone | | | 0.236‡ |
| Yes | 7(38.9) | 11(61.1) | |
| No | 6(66.7) | 3(33.3) | |
| Furosemide | | | 0.082† |
| Yes | 4(30.8) | 9(69.2) | |
| No | 9(64.3) | 5(35.7) | |
| Methylprednisolone | | | 1.000‡ |
| Yes | 4(50.0) | 4(50.0) | |
| No | 9(47.4) | 10(52.6) | |

*Seven medical records were excluded from this analysis due to lack of record of information concerning emergency interventions; †Chi-square test; ‡Fisher's exact test; §Nine medical records were excluded from the analysis of the outcomes of medication with survival, in view of the lack of record of information

## Discussion

Regarding the limitations of the study, the small sample size plus the fact that the study was retrospective and single center made it impossible to generalize the results. Moreover, the lack of articles dealing with herbicide poisonings in Brazil, especially by paraquat herbicide in the last five years made it impossible to contextualize the results with national data.

Thus, the findings revealed significant data that were obscured until the conclusion of this research, i.e., in the state of Rondônia, there is no Center for Information and Toxicological Assistance, which further increases the chance of underreporting, thus, it is possible, based on these more reliable results, that managers can adopt public and collective health strategies in order to implement monitoring and preventive epidemiological surveillance effectively to avoid harm to victims of poisoning mainly by paraquat due to its high toxic power, besides this substance being considered a lethal weapon for self-extermination.

It is observed that, in general, the results of the study bring significant contributions to nursing, so that nurses can implement the nursing process in a safe and effective way, seeking, in this sense, the brevity in the evaluation of clinical manifestations and the quick inactivation of the agent before the generalized biocide action and reduce the lethality considerably either in the emergency unit or intensive care.

The clinical features of acute paraquat intoxication are characterized by high mortality, rapid progression, and frequent lesions in the lung and kidneys. These characteristics were evident in this study and are in line with the results presented by researchers[11], for whom paraquat causes significant organ damage, the most affected being the lungs and kidneys. In addition, the emergency care measures evaluated in this study were not effective in increasing survival, as well as any medication used to treat intoxicated patients.

Similarly, the respiratory and renal systems were most affected in this study. The initial toxicological effects of paraquat on the lungs promote the des-

truction of alveolar type I and type II epithelial cells caused by cyclic oxidative stress, damage to which impairs gas exchange and surfactant secretion, producing hypoxia and edema respectively[11].

Therefore, in this study, as well as in a research conducted in Iran[12], respiratory distress, dyspnea, tachypnea, and hypoxemia were significantly more frequent in fatal cases than in surviving patients. These patients may also progress to severe pneumonia and pulmonary fibrosis that often leads to death within a few weeks[5,12]. The severe oxidative damage caused by paraquat intoxication is not restricted to the lungs and kidneys, but also affects other organs such as the liver, causing tissue inflammation, edema, and liver fibrosis[3]. These cases usually result in acute renal failure, acute hepatitis, and collapse of the cardiovascular system, leading to multiple organ failure and cardiogenic shock within one to four days[2,4,13].

Our results showed that paraquat intoxication leads to an increase in the hepatic biochemical markers aspartate transaminase and alanine transaminase. The above-mentioned hepatic enzymes are found in plasma and in various tissues but are most abundant in the liver. Thus, these enzymes are considered indicators of liver tissue damage. The significant increase in transaminase activity in paraquat intoxicated patients can be explained by destructive changes in liver cells[12,14]. They are, therefore, efficient biomarkers and usual clinical indices to assess liver function[14]. Thus, in relation to liver function, significant differences were found in patients who died when compared to the survival group, indicating that more attention to liver protection with specific medication may be needed.

Prevention of absorption as an important emergency response was highlighted in a survey of 62 patients in French Guiana[15] as paraquat is rapidly absorbed from the gastrointestinal tract. According to the toxicokinetic of paraquat, this approach would be most effective if applied within four hours of ingestion. Generally, measures used to prevent absorption of paraquat include induction of vomiting with emetic substances or by mechanical stimulation, gastric lavage, and administration of adsorptive substances such as activated charcoal and Fuller's Earth[8,13].

However, despite being widely used methods, these emergency care measures have not been shown to be effective in several studies, demonstrating a lack of correlation between absorption prevention and increased survival[16-17]. In fact, most patients in this study received gastric lavage with activated charcoal and Fuller's Earth, but there was no significant relationship with patient survival.

Emergency care measures for acute paraquat poisoning also include removal of blood by extracorporeal purification. Hemoperfusion is a technique that removes paraquat from the blood and that may improve the prognosis and survival of some patients[18-19]. However, its effectiveness depends on timing and early therapy, as demonstrated by a study in which hemoperfusion was shown to be very effective, but with a rescue window of less than four hours[16].

Hemodialysis is also used to purify the bloodstream in paraquat intoxicated patients, but the rate of reduction of its plasma levels by hemoperfusion is greater than by hemodialysis[18-19]. In this study, hemodialysis was negatively correlated with patient survival. These patients were probably outside the therapeutic window or had severe intoxication[16], causing hemodynamic instability leading to cardiovascular failure, which was the third most frequent cause of death in this study.

In relation to pharmacological measures with patient survival, there are some improvements reported for patients treated with antioxidants, anti-inflammatory drugs and immunosuppressants[15]. On the other hand, the efficacy of several different drugs for paraquat poisoning has been extensively studied and reviewed, and most studies have not found a direct correlation between any class of drug and survival of severely poisoned patients[2,15].

The correlation between survival and medication may be related to the effectiveness of emergency care measures that can increase survival by increasing

the time and chance for the medication to act in the body. The action of medication is slow, because many processes of tissue damage are already in progress and may take time to reverse. The most prescribed classes of drugs in this study were not successful in improving patient survival. This lack of effect of any medication may also be related to other underlying factors such as the amount ingested and the initial time to emergency care[16].

The initial interventions by the multi-professional team should be fast and appropriate, because the rapidity of diagnosis and early treatment are decisive in the clinical evolution and outcome of cases[20]. In this sense, it is essential the role of nurses in the care of victims of exogenous poisoning through systematized actions focused on containing the progression of the toxic by the victim's body.

The results of the study pointed out potentialities for nursing care that go from admission to discharge. In this patient profile, the passage of a gastric lavage tube, venous puncture, among other measures, such as neurological, cardiac, respiratory, and renal control through monitoring of urine output are actions for which the nurse needs to increase vigilance, seeking to reestablish the physiological integrity of the affected systems as soon as possible for survival.

## Conclusion

It is possible to observe in the study that paraquat intoxication victims have a considerable chance of dying, especially when the ingestion is above 50ml, and although the number of deaths was lower than the number of survivors, all the victims who died were victims of attempted self-extermination. In addition, no emergency care measures such as gastric lavage with activated charcoal and Terra Fuller through a tube, hemodialysis, oxygen therapy, medication such as acetylcysteine, hydrocortisone, methylprednisolone, ascorbic acid and furosemide, used worldwide in cases of paraquat poisoning were effective in increasing survival.

We conclude that, among all the functional systems of the human body, the most compromised were the respiratory, renal, and hepatic systems, showing that paraquat has a strong tropism for these organs. Although it is still possible to monitor the affected systems by means of clinical symptoms and biochemical markers, mortality is still high, more specifically in cases of suicide attempts.

## Collaborations

Souza LP contributed to the conception, planning, analysis, interpretation and writing of the research, relevant critical review of the intellectual content and approval of the final version to be published. Vasconcellos C contributed to the analysis, interpretation, writing of the article and approval of the final version to be published. Romanholo RA contributed to the analysis, interpretation of the data, and writing of the article.

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