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Peripheral burning sensation: a novel clinical marker of poor prognosis and higher plasma-paraquat concentrations in paraquat poisoning

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Introduction. Self-poisoning with paraquat has a case fatality ratio (CFR) over 65% in Sri Lanka. Plasma-paraquat concentration is the best prognostic indicator for patient outcome but is not readily available. Alternative surrogate clinical markers could be useful in management and determining prognosis. Anecdotal reports by medical and research staff suggested that patients who complained of burning sensation of the body had a poor prognosis and a prospective study was initiated. **Methods.** This was a prospective observational study in three hospitals in Sri Lanka. We collected demographic data, presence or absence of burning sensation, and major outcome, and determined the plasma-paraquat concentration within 24 h post-ingestion. **Results.** There were 179 patients with deliberate self-ingestion of paraquat over 30 months. Burning sensation was reported in 84 patients (48%), which was initiated at a median of 1 day (range 1–3 days) post-ingestion. Of the patients who had burning, 61 died [CFR = 72.62%; 95% confidence interval (CI) = 62–81]. Of the 91 patients who had no peripheral burning, 23 died (CFR = 25.27%, 95% CI = 18.15–35.9). Presence of peripheral burning sensation was associated with a significantly higher risk of death (odds ratio = 7.8, 95% CI = 3.9–15, $p < 0.0001$). Patients who complained of peripheral burning died at a median of 36 h (interquartile range = 30.5–88) following ingestion whereas those who had no peripheral burning died at a median of 50.5 h (interquartile range = 16.75–80). The difference was not significant ($p > 0.05$). Median admission plasma-paraquat concentration in patients with peripheral burning (2.67 $\mu\text{g/mL}$, 95% CI = 0.84–14.2) was significantly higher than in the patients with no peripheral burning (0.022 $\mu\text{g/mL}$, 95% CI = 0.005–0.78; $p < 0.001$). Peripheral burning has a sensitivity of 0.72 (95% CI = 0.6–8) and specificity of 0.74 (95% CI = 0.64–0.08) and a positive predictive value of 0.73 (95% CI = 0.6–0.8). **Discussion.** It is possible that this symptom may help discriminate between patients who have poor chance of survival and those who may potentially benefit from interventions. The mechanism is not clear but could either include a direct concentration-related effect or be a marker of oxidative stress. **Conclusion.** Presence of burning sensation is associated with high plasma-paraquat concentrations and is strongly predictive of death.

Keywords Self-poisoning; Herbicide; Risk assessment

Introduction

Self-poisoning with pesticides is a major public health problem across the Asia-Pacific Region.¹ It is estimated that globally 250,000–370,000 people die from pesticide poisoning each year.² Sri Lanka has a major problem with intentional self-poisoning with high total and youth suicide rates.³ Self-poisoning is the fourth leading cause of death in some regions of Sri Lanka.⁴ Overall, self-poisoning in Asia has a relatively high case fatality ratio (CFR) (10–20%)⁵ whereas paraquat

self-poisoning has the highest individual CFR (~65%) for any given poison in Sri Lanka.⁶

The best prognostic marker that has been shown to predict mortality to date is the plasma-paraquat concentration with acceptable sensitivity and specificity.^{7–9} Measurement of plasma-paraquat concentration is not available in Sri Lankan hospitals.

While conducting two research studies on paraquat toxicity (prospective observational study and a randomized controlled clinical trial) in Sri Lanka, medical and research staff noted that patients who complained of burning sensation of the skin of trunk and limbs (described as if their skin was on fire) seemed more likely to die. This symptom was not previously described and was distinctly different from the epigastric burning sensation commonly experienced by patients who have ingested paraquat. The symptom was termed “peripheral burning sensation” to differentiate it from the burning epigastric

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Table 1. Demography and outcome

	Group with peripheral burning n = 84 [males: 66 (78.6%)]	Group with no peripheral burning n = 91 [males: 68 (74.7%)]	Significance
Age (years) (range)	28.5 (21–37)	26 (21–38)	Not significant
Admission plasma-paraquat concentration, median, and IQR ($\mu\text{g/mL}$)	2.7 (0.81–13) n = 48	0.02 (0.005–0.78) n = 49	Significant (p < 0.001)
Number of deaths	61	23	
Case fatality rate	72.6% (95% CI = 62–81)	25.27% (95% CI = 18.15–35.9)	Significant (p < 0.05)
Time to death and IQR (h)	39.2 (30.5–93.6)	50 (9–81)	Not significant

pain. The objectives of the study were to examine the predictive value of peripheral burning sensation for death following self-ingestion of paraquat and to examine its correlation with admission plasma-paraquat concentration.

Methods

Ethical approval for both studies (observational study and the randomized controlled clinical trial) was obtained from the Ethics Review Committees of Sri Lanka Medical Association, Faculties of Medicine of Peradeniya and Ruhuna, and Australian National University. All paraquat self-poisoning patients who presented to three study hospitals in Sri Lanka from January 2006 to July 2008 and who were able to give a history were asked for the presence or absence of peripheral burning sensation on a twice daily basis by medically qualified (doctors) research assistants. A plasma sample was taken soon after admission. Samples were stored frozen and sent to Syngenta CTL (Alderley Park, Macclesfield, Cheshire, UK) for the determination of paraquat ion concentration using high-performance liquid chromatography, liquid chromatography mass spectrophotometry (LC–MS–MS), and LC fluorescence.¹⁰ Patients were followed up until death or discharge. Patients discharged from hospital were visited at their homes after 3 months and outcome recorded. All out of hospital deaths were confirmed by examination of the death certificate issued by the registrar of deaths.

Data were entered into an excel worksheet and analyzed using Stata (version 10.1, Stata Corp. 2001; Statistical Software: Release 7.0, College Station, TX, USA) and Graph Pad Prism (version 4.03 for Windows; GraphPad Software, San Diego, CA, USA). Parametric data were analyzed using unpaired *t*-test whereas nonparametric data were compared using χ^2 and Mann–Whitney Test.

Results

There were 179 patients with deliberate self-ingestion of paraquat from January 2006 to June 2008. Four patients were excluded as they were too unwell to respond to verbal commands. There were 84 deaths giving an overall CFR of 48%. Five

different commercial preparations containing 200 g/L were used for self-ingestion [X press[®], One shot[®], Gramoxone[®], Gramoxone Inteon[®] (containing additionally a purgative and an alginate that form a gel on contact with stomach acid) and Baur's paraquat[®]] by the patients (Table 1).

Peripheral burning sensation was observed in 84 patients (48%), which was initiated at a median of 1 day (range 1–3 days) post-ingestion. Of the patients who had burning, 61 died [CFR = 72.62%; 95% confidence interval (CI) = 62–81]. Of the 91 patients who had no peripheral burning, 23 died (CFR = 25.27%, 95% CI = 18.15–35.9) (Fig. 1).

Presence of peripheral burning sensation was associated with a significantly higher risk of death (odds ratio = 7.8, 95% CI = 3.9–15, p < 0.0001). Patients who complained of peripheral burning died at a median of 36 h [interquartile range (IQR) = 30.5–88] following ingestion whereas those who had no peripheral burning died at a median of 50.5 h (IQR = 16.75–80). The difference was not significant (p > 0.05).

Peripheral burning has a sensitivity of 0.72 (95% CI = 0.6–8) and specificity of 0.74 (95% CI = 0.64–0.83) and a positive predictive value of 0.73 (95% CI = 0.6–0.8) in predicting death following self-poisoning with paraquat.

Admission plasma-paraquat concentration was available in 49 patients who had no peripheral burning sensation and in 48 patients who had peripheral burning sensation. Median admission plasma sampling time was 8.3 h (IQR = 4.21–13.25). Median admission plasma-paraquat concentration in

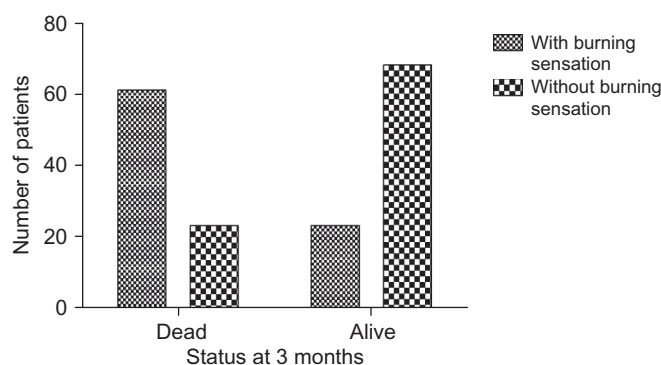


Fig. 1. Outcome of patients with burning and without burning sensation.

patients with peripheral burning (2.67 $\mu\text{g/mL}$, 95% CI = 0.84–14.2) was significantly higher than in the patients with no peripheral burning (0.022 $\mu\text{g/mL}$, 95% CI = 0.005–0.78; $p < 0.001$). There was no significant difference ($p > 0.05$) in admission plasma-paraquat concentrations and time to death in the deceased patients in the two groups.

Discussion

The mechanism of this symptom is not clear. It is possible that the peripheral burning sensation is because of a primary effect of paraquat on peripheral nociceptive nerve fibers or as a result of paraquat-induced oxidative stress that causes lipid peroxidation, mitochondrial toxicity, activation of nuclear factor kappa B (NF- κ B), and cell death.^{11–14} One of the causes of nociceptive pain is tissue inflammation. Generation of free radicals induces inflammation of tissues, including skin, which may stimulate nociceptors. Further studies to correlate this symptom with quantification of oxidative stress generated should be carried out.

Peripheral burning sensation has a clinically useful sensitivity as a bedside marker of prognosis following paraquat self-ingestion in resource poor settings. This may be clinically useful particularly in settings where laboratory-based prognostic markers are not readily available and could potentially assist in discriminating between patients who have no chance of survival and those who may potentially benefit from interventions in clinical trials using investigational antidotes such as immunosuppression with dexamethazone, cyclophosphamide, and methylprednisolone. A bedside prognostic marker could improve stratification of patients in clinical trials and reduce the potential bias of post hoc stratification.

Our study excluded a small ($n = 4$) group of patients who were unable to give a history on admission. We did not attempt to grade the severity of the symptom by examining pain scores or the extent of symptoms. Further studies should examine whether there is possible grading of severity of peripheral burning which may be clinically useful. A severity score should be designed and its correlation with biochemical changes such as liver and renal impairment, severity of oxidative stress, and magnitude of hypoxia should be studied. Another limitation is that the researchers were not blinded to the study hypothesis that should be addressed in a future study. However, plasma-paraquat concentrations were significantly higher in the group with peripheral burning which implies that this bias may have been minimal.

Conclusion

Presence of burning sensation is associated with high plasma-paraquat concentrations and is strongly predictive of death. The cause of this new symptom is unknown and warrants further study.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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