

Cleistanthus collinus poisoning: experience at a medical intensive care unit in a tertiary care hospital in south India

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Background & objectives: Ingestion of *Cleistanthus collinus* causes hypokalemia and cardiac arrhythmias leading to mortality in most cases. We undertook this retrospective study to evaluate the clinical presentation and predictors of outcome in critically ill patients admitted with *C. collinus* poisoning.

Methods: The case records of 56 patients admitted to the medical intensive care unit (MICU) of a tertiary care teaching hospital in south India (2000-2014) with *C. collinus* poisoning were retrospectively analysed.

Results: The mean age of patients was 36.7±13.3 yr; there were 30 males. Salient clinical manifestations included hypokalemia (58%), neutrophilic leucocytosis (48.2%), acute kidney injury (AKI) (42.9%), acute respiratory failure requiring mechanical ventilation (AcRFMv) (32.1%), shock (21.4%); cardiac arrhythmias and neuromuscular weakness (19.6% each); 21 patients (37.5%) had adverse outcome. Longer time-lapsed from consumption to reaching emergency room [median (interquartile range)] (hours) [49 (22-97) vs. 28 (7-56), $P=0.038$]; higher acute physiology and chronic health evaluation II (APACHE II) score at presentation [14 (8.25-14.75) vs. 2 (0-6) $P<0.001$]; and presence of the following [odds ratio (95% confidence intervals)] at initial presentation: shock [37.40 (4.29-325.98), $P=0.001$]; AcRFMv [26.67 (5.86-121.39), $P<0.001$]; elevated alanine aminotransferase [5.71 (1.30-25.03), $P=0.021$]; metabolic acidosis [5.48 (1.68-17.89), $P=0.005$]; acute kidney injury (AKI) [5 (1.55-16.06), $P=0.007$]; hyponatremia [4.67 (1.25-17.44), $P=0.022$]; and neutrophilic leucocytosis [3.80 (1.02-14.21), $P=0.047$] predicted death. A significant ($P<0.001$) increasing trend in mortality was observed with increasing International Program on Chemical Safety Poisoning Severity Score (IPCS-CSS) grade.

Interpretation & conclusions: *C. collinus* is a lethal poison associated with high mortality for which there is no specific antidote. Careful search and meticulous monitoring of the predictors of death and initiating appropriate corrective measures can be life saving.

Key words Acute kidney injury - acute respiratory failure - APACHE II - *Cleistanthus collinus* - outcome - poisoning

Cleistanthus collinus, a plant belonging to the family *Euphorbiaceae* is commonly encountered in the south India¹. All parts of this plant are poisonous. *C. collinus* is a commonly used suicidal poison with the victims intentionally ingesting any part of the plant (usually leaves)¹. Mortality with *C. collinus* is about 30 per cent with death occurring in 3-7 days following ingestion². The toxic active ingredients in leaves of this plant are aryl naphthalene lignan lactones, namely, diphyllin and its glycoside derivatives cleistanthin A, cleistanthin B; and collinusin³. Ingestion of this plant causes hypokalemia and cardiac arrhythmias peaking on the third or fourth day of ingestion. Mortality may result from arrhythmias, renal failure, shock or respiratory failure⁴. However, the pathogenetic mechanisms of toxicity are poorly understood till date. The present study was undertaken to document the clinical presentation and predictors of outcome in patients with *C. collinus* poisoning seen in a tertiary care hospital in south India.

Material & Methods

The case records of 56 patients diagnosed to have and treated for *C. collinus* poisoning during the period April, 2000 to October, 2014 at the Sri Venkateswara Institute of Medical Sciences (SVIMS), a tertiary care teaching hospital in Tirupati, Andhra Pradesh, India, were retrospectively studied. The study was approved by the Institutional Ethics Committee.

At the time of initial evaluation in the emergency room (ER), all patients received gastric lavage, and symptomatic treatment including intravenous (iv) fluids, inotropic support, correction of electrolyte abnormalities, metabolic acidosis; anti-arrhythmic therapy, renal replacement therapy and assisted mechanical ventilation, among others if needed. Following initial stabilization in the ER, they were transferred to the medical intensive care unit (MICU) for further management. On admission, the following investigations were done: portable chest radiograph, 12-lead electrocardiogram (ECG); complete haemogram, serum biochemistry and arterial blood gases.

In all of them the following data were recorded in a case record form: demographic data; details of plant part used and method of consumption for poisoning; time-lag between consumption of the poison and arrival at the ER, acute physiology and chronic health evaluation II (APACHE II) score⁵, laboratory characteristics; need for assisted mechanical ventilation, duration

of mechanical ventilation; duration of MICU stay, hospital stay; and treatment outcome. In all patients International Program on Chemical Safety Poisoning Severity Score (IPCS-PSS)⁶ was also calculated at the time of admission to MICU. The IPCS-PSS⁶ allows grading of the severity of acute poisonings regardless of the type and number of agents involved. As per the IPCS-PSS⁶, the severity of poisoning at the time of initial presentation was graded as grades 0 (none), 1 (mild), 2 (moderate), 3 (severe).

Statistical analysis: To identify predictors of death in patients with *C. collinus* poisoning at the time of initial presentation, univariate analysis was carried out to compare the demographic, clinical, and laboratory variables between patients who were alive and dead using unpaired t test, Mann-Whitney U-test for continuous variables and chi-square test, odd's ratio (95% confidence intervals) for categorical variables. All tests were two-tailed. For the purposes of statistical analysis, patients who had "left against medical advice" were considered to have worst outcome *i.e.* "death". Statistical softwares IBM SPSS, Version 20, (IBM SPSS Statistics, Somers NY, USA); and MedCalc Version 11.3.0 for Windows 2000/XP/Vista/7 (MedCalc Software bvba, Belgium) were used for statistical analysis.

Results

Their mean age was 36.7±13.3 yr (range 14 to 70 yr); there were 30 males. Thirty nine patients took the boiled extract/decoction of leaves, six took the crushed leaves sweetened with jaggery (traditional unrefined brown sugar made from concentrated sugar cane juice), seven consumed raw leaves and four consumed fruits and seeds of *C. collinus* plant. Median [interquartile range (IQR)] time-lapsed from consumption to reaching ER was 32 (IQR 8.25-63.5) hours. Salient clinical manifestations observed at the time of admission included acute kidney injury (AKI) [n=24 (42.9%)], acute respiratory failure requiring mechanical ventilation (AcRFMv) [n=18 (32.1%)], shock [n=12 (21.4%)], cardiac arrhythmia and neuromuscular weakness [n=11 (19.6%)]. Myasthenic crisis-like syndrome was observed in one patient⁷.

Laboratory abnormalities evident at the time of admission included hypokalemia in 58 per cent (29/50), hyponatremia 28 per cent (14/50), and neutrophilic leucocytosis in 54 per cent (27/50) patients. APACHE II score was available for 55 of

the 56 patients studied; APACHE II score could not be computed in one patient as he died within an hour of arrival in the ER. Median APACHE II score at the time of initial presentation was 5 (IQR 1-14). As per the IPCS-PSS, the severity of poisoning at the time of initial admission was observed to be grade 0 (n=5, 8.9%); grade 1 (n=19, 33.9%); grade 2 (n=13, 23.2%); and grade 3 (n=19, 33.9%).

Median durations of MICU and total hospital stay were three (IQR 1-5) and four (IQR 2-6) days, respectively. Median duration of mechanical ventilation in patients with AcRFMv was nine (IQR 4-71.5) h. Seventeen patients died. Four of the severely ill patients sought discharge from the hospital against medical advice. Fourteen of 17 patients died within seven days of consumption of *C. collinus*.

On univariate analysis, the following variables were found to be significant predictors of death: longer median time-lag from consumption to reaching the ER ($P=0.038$); higher median APACHE II score at presentation ($P<0.001$) (Table I); presence of shock ($P=0.001$); AcRFMV ($P<0.001$); elevated alanine aminotransferase ($P=0.021$); metabolic acidosis ($P=0.005$); AKI ($P=0.007$); hyponatremia ($P=0.022$); and neutrophilic leucocytosis ($P=0.047$) (Table II). An increasing trend was seen in mortality with increasing IPCS-CSS severity. None of the patients with IPCS-PSS grade 0 (n=5) died; one of the 19 patients with grade 1 severity; six of the 13 patients with grade 2 severity; and 14 of the 19 patients with grade 3 (73.7%) severity died ($P<0.001$).

Discussion

There are only a few published human studies^{1,4,8-10} available on *C. collinus* poisoning. However, in these studies severity of illness scoring systems was not used.

C. collinus is commonly used for acute deliberate self-poisoning in south India^{1,2,4,7,8,10} including the Rayalaseema area of Andhra Pradesh State where Tirupati is located. In the present study, the patients were older when compared with the patients seen at Vellore, India^{8,9}. Consumption of *C. collinus* was found equal among women and men (male:female=1.1:1) in the present study while in other studies a female preponderance was observed. Metabolic acidosis, the most common clinical manifestation in two earlier reports from Puducherry (21.7%)¹ and Vellore (100%)⁹ was only observed in 32 per cent of patients in the current study. Hypokalemia (58%) was the most common clinical feature in our patients which was similar to the figure documented in earlier reports^{8,10}. Hypokalemia can be due to vomiting, and probable renal tubular loss of potassium associated with severe metabolic acidosis⁸. Hyponatremia was found to be a predictor of death in the present study as also reported in an earlier study¹. Cardiac arrhythmia was seen in 19.6 per cent of our patients at presentation, which could have resulted from hypokalemia, direct effect of the poison on myocardium and also possible direct cardiodepressant effect of the plant toxins¹¹. An interesting observation was myasthenic crisis like syndrome with ptosis, dysphagia and neuromuscular weakness in a patient who required ventilator support⁷. In this patient, predominant neuromuscular manifestations were potentially reversible with neostigmine which resulted in a striking improvement. Animal experimental data seem to support the use of neostigmine in patients with *C. collinus* poisoning who develop myasthenic syndrome. In Albino rat model, injecting lethal dose 50 (LD₅₀) of leaf extracts of *C. collinus* intraperitoneally caused neuromuscular junctional blockade at postsynaptic acetylcholine receptors resulting in decremental response which was potentially reversible with the administration of neostigmine and aminopyridine¹²⁻¹⁵.

The presence of neutrophilic leucocytosis, hypokalemia, metabolic acidosis, cardiac arrhythmia, neuromuscular weakness and respiratory failure suggests that *C. collinus* is a systemic poison with multitude of effects^{4,8}. The vomiting and severe

Table I. Comparison of continuous variables between survivors and non-survivors with *Cleistanthus collinus* poisoning

Variable	Dead (n=21)	Alive (n=35)
Age (yr) (mean ± SD)	38.8 ± 13.9	35.4 ± 13
Time-lapsed from consumption to reaching ER (h) [median (IQR)]	49 (22-97)	28 (7-56)*
APACHE II score† [median (IQR)]	14 (8.25-14.75)	2 (0-6)***

†Available for 19 patients; one patient died within an hour of arrival in the emergency room.

ER, emergency room; APACHE, acute physiology and chronic health evaluation; IQR, interquartile range

$P^* < 0.038$, $*** < 0.001$ compared to dead

Table II. Comparison of categorical variables between survivors and non-survivors with *Cleistanthus collinus* poisoning

Variable	Observation	Dead (n=21)	Alive (n=35)	Odds ratio (95% CI)	P value
Gender	Male	14	16	2.37 (0.77-7.31)	0.132
	Female	7	19		
Cardiac arrhythmia	Present	5	4	2.67 (0.62-11.38)	0.185
	Absent	15	32		
Metabolic acidosis	Present	13	8	5.48 (1.68-17.89)	0.005
	Absent	8	27		
AKI	Present	14	10	5.00 (1.55-16.06)	0.007
	Absent	7	25		
Shock	Present	11	1	37.40 (4.29-325.98)	0.001
	Absent	10	34		
AcRFMv	Present	15	3	26.67 (5.86-121.39)	<0.001
	Absent	6	32		
Neuromuscular weakness	Present	8	3	6.56 (1.50-28.70)	0.012
	Absent	13	32		
Hypokalemia*	Present	12	17	3.00 (0.80-11.19)	0.102
	Absent	4	17		
Hyponatremia*	Present	8	6	4.67 (1.25-17.44)	0.022
	Absent	8	28		
Neutrophilic leucocytosis*	Present	12	15	3.80 (1.02-14.21)	0.047
	Absent	4	19		
Hyperbilirubinaemia†	Present	1	5	0.40 (0.04-3.86)	0.428
	Absent	11	22		
Aspartate aminotransferase†	Elevated	11	15	8.80 (0.99-78.11)	0.051
	Normal	1	12		
Alanine aminotransferase†	Elevated	8	7	5.71 (1.30-25.03)	0.021
	Normal	4	20		

*n = 50, †n = 39, AKI, acute kidney injury; AcRFMv, acute respiratory failure requiring mechanical ventilation

abdominal pain noticed on the first day of ingestion implicates the direct effect of the poison on the gastric mucosa. The usual causes of death are respiratory failure requiring ventilator support and cardiac arrhythmia^{4,8}. In the present study, 37.5 per cent mortality was observed which was higher than that observed in earlier reports^{1,4,8-10}. This difference may be because of older age and delayed presentation to hospital in the present study.

In a study from Vellore⁷, Cox regression modelling revealed mode of ingestion, older age and history of chronic disease as predictors of death, while higher plasma potassium levels were associated with a significant 58 per cent risk reduction in mortality per 1 mmol/l increase in plasma potassium level. In the present study, longer median time-lag from consumption to reaching the ER; higher median APACHE II score

at presentation, presence of shock, AcRFMV, elevated alanine aminotransferase, metabolic acidosis, AKI, hyponatremia and neutrophilic leucocytosis were predictors of death. By identifying and correcting these factors and instituting early and aggressive supportive management, there is a potential to reduce mortality in patients with *C. collinus* poisoning.

Further prospective studies are required to elucidate the clinical manifestations of *C. collinus* poisoning. Further research is also needed to understand the mechanisms of toxicity as well as for the development of potential antidotes, to reduce mortality. Careful search and meticulous monitoring of the predictors of death and early initiation of appropriate corrective measures can be life-saving.

Conflicts of Interest: None.

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