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Original article

A retrospective comparison of the burden of organophosphate poisoning to an Intensive Care Unit in Soweto over two separate periods

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ABSTRACT

Introduction: Organophosphate poisoning (OPP) is a major health-care burden in South Africa. Recently, we have observed that patients admitted to our Intensive Care Unit (ICU) with OPP have followed a more complicated course in comparison to previous years.
Objectives: To describe the differences in the clinical course and costs of patients with OPP between two time periods, namely 2012 and 2017.
Methods: Retrospective comparison of patients admitted to the Intensive Care Unit (ICU) of Chris Hani Baragwanath Academic Hospital between January 2012 to December 2012 and January 2017 to December 2017.
Results: Forty-one patients were found in the database. Patients from our 2017 cohort showed a significantly longer total median (IQR) length of stay 8 (4–17) days vs. 2 (2–3) days, p = 0.000, duration of antidote therapy 5 (3−10) days vs. 2 (2–3) days, p = 0.004 and duration of ventilation 4 (2−11) days vs 1 (1–2) day, p = 0.003. Patients presenting in 2017 were more likely to be admitted to ICU, odds ratio 5.6 (CI 1.2–26). There was a 31-fold increase in ICU costs between 2012 and 2017.
Conclusion: Based on our experience, the clinical course of OPP requiring ICU admission has evolved into a condition with a longer length of stay, duration of antidote therapy, ventilatory support, increased risk of complications and additional costs.

African relevance

- Organophosphate poisoning has been a public health problem for decades in Africa.
- There is poor regulation of organophosphate compounds in low-resourced regions such as Africa.
- We demonstrate a new clinical presentation of organophosphate poisoning, reflecting a possible new compound.
- There is an urgent need to strengthen surveillance systems locally and regionally.

Introduction

Organophosphates are mainly used as pesticides in the farming industry but also in commercial and domestic buildings. Organophosphate poisoning (OPP) is a major health-care burden with the World Health Organization (WHO) estimating 200,000 related deaths per year, mainly in the Asia-Pacific region [1]. The incidence and mode of organophosphate poisoning varies considerably between countries and the true extent of the problem in South Africa is uncertain due to under-reporting. Anecdotally, OPP is likely the most common cause of admissions into our ICU due to poisoning from drugs and toxin ingestion.

In developed countries, the incidence is 18.2 per 100,000 through accidental occupational exposure [2]. On the other hand, in developing countries, cases of OPP are mainly intentional and the incidence is much higher, with figures as high as 180 per 100,000 in Sri Lanka [3]. This has been attributed to the lack of regulation and low cost of organophosphate compounds in developing countries. Locally, a recent study showed that between 2012 and 2014 in the Tshwane district 51% of OPP cases were intentional, 21.7% cases unintentional and 26.5% unknown. [4]

Organophosphates inhibit an enzyme called acetylcholinesterase which serves to degrade acetylcholine at neuromuscular junctions in the peripheral and central nervous system. The net effect of this inhibition is an accumulation of acetylcholine which results in unopposed activation of the parasympathetic nervous system and stimulation at the neuromuscular junctions. The clinical manifestations depend on the site of stimulation. Some of most common muscarinic features are: miosis,

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bronchorrhoea, diarrhoea, hypotension, bradycardia, and some of the most common nicotinic features are fasciculations, hypertension and tachyarrhythmias [5–7].

Numerous prognostic factors have previously been described, the type of toxin (carbamate vs. organophosphate), severity of poisoning, delay in starting treatment and duration of ventilation [8,9]. The development of complications such as ventilator associated pneumonia and aspiration pneumonitis are often responsible for respiratory failure, prolonged ventilation and poor outcomes [10].

Recently, we have observed that patients admitted to our Intensive Care Unit (ICU) with OPP have followed a more complicated course in comparison to previous years. Based on this observation, we set out to investigate the differences in the course of the disease and associated costs between the two time periods, namely; 2012 and 2017.

Methods

Setting

A retrospective review of the ICU database at Chris Hani Baragwanath Academic Hospital over 2 periods, 2012 and 2017. The choice of the two time periods was made based on the timing of the market withdrawal of aldicarb (a carbamate) by a large manufacturer. We included adult patients, 18 years and older, admitted to the ICU with a diagnosis of OPP. We excluded all cases of polypharmacy overdose.

Ethical considerations

Ethical approval to perform the study was obtained from the Human Research Ethics Committee (Medical) of the University of Witwatersrand (M171114). Informed consent was waived due to the retrospective nature of this study.

Data collection

Data from patient's files and databases was collected and recorded. The following patient information was collected: age, gender, symptoms on presentation, development of complications, duration of interventions, length of stay (LOS) was defined as total length of stay in ICU and high care (HCA), cost of stay (COS) and ICU mortality. The number of courses of antibiotics (AB No) was used as a surrogate marker of infectious complications in the ICU. Documented complications included aspiration pneumonitis, ventilator associated pneumonia (VAP), cardiac arrest, ICU acquired weakness, tracheal stenosis and seizures. The presence of documented complications was treated as a binary variable (present/absent). Re-intubation and requirement for tracheostomy were also considered as complications.

Outcomes

The primary outcome was the length of stay in ICU. Secondary outcomes included; duration of antidote therapy, duration of ventilation, complications, proportion of patients admitted to ICU, monthly incidence and associated ICU costs.

Statistical analysis

We calculated sample size (n) based on an initial estimated proportion of 10% of patients staying in ICU for 7 days or more in 2012 and an increase to 35% requiring this prolonged ICU LOS in 2017. Using a 5% level of significance and 90% power, the minimum required sample size was 30. Data was analyzed for distribution and appropriate non-parametric statistical analysis performed. Median and interquartile range (IQR, Q1-Q3) was used for continuous data and percentages for dichotomous data. The Mann-Whitney *U* test was used to compare independent medians and the Chi-square/Fisher exact test for proportion/percentages. Daily ICU costs in South African Rands (ZAR) were based on published estimates in 2 South African (tertiary/Quaternary) ICU's in 2016 and were applied to the median number of ICU days to calculate the ICU cost per patient in 2012 and 2017 [11]. Annual ICU costs were estimated by further applying this to the total number of ICU admissions in each period. All costs are reported in 2016 prices. A 5% level of significance was used. Data was analyzed using Statistica version 13.3 (StatSoft, USA).

Results

A total of 41 patients were found in the database. Nine patients were admitted during the 2012 period and 32 OPP patients during the 2017 period. There were 22 (54%) males. The median age of the entire group was 26.5 years. In terms of presentation, all patients (100%) in both time periods presented with a cholinergic toxidrome of symptoms. Patient characteristics are provided in Table 1.

Primary outcome

Patients from our 2017 cohort showed a significantly longer total length of stay which included ICU and HCA stay when compared to the 2012 period. Table 2 provides details on the length of stay.

Secondary outcomes

Duration of antidote therapy and duration of ventilation

There was a significantly longer duration of antidote therapy in 2017 compared to the 2012 period. Details provided in Table 2. Ventilator days were also significantly greater in 2017 when compared to 2012. See Table 2.

Complications

A comparison of the complications over the two periods is given in Table 3. There was a trend towards an increase in the number of complications in the 2017 period with no statistical difference noted for any complication. The total number of complications was 5 among 9 patients in 2012 compared to 57 among 32 patients in 2017.

Proportion of OPP cases admitted to the ICU

In 2012, 222 patients presented to the medical emergency unit with a diagnosis of OPP compared to 168 patients in 2017. The percentage of ICU admissions in 2017 was 19% (32/168) compared to 4% (9/222) in 2012. The odds of requiring ICU admission were significantly higher in 2017 compared to 2012, OR 5.6 (Confidence Interval 1.2–26).

Monthly incidence

The monthly incidence for the 2 periods is given in Fig. 1. Three peaks are identified during December, March/April and August.

ICU costs

In terms of cost, there was a 31- fold increase in ICU costs between 2012 and 2017, shown in Table 4.

Table 1
Characteristics of patients admitted with OPP over the 2 periods.

	All patients	2012 patients	2017 patients
No of admissions	41	9 (22%)	32 (78%)
Male patients	22 (54%)	5 (56%)	17 (53%)
Age(y) Median (IQR)	26.5 (22–34.5)	27.5 (22–37.5) (n = 8)	26 (21.5–34.5)
Cholinergic Sx	39/39 (100%)	9/9 (100%)	30/30 (100%)
Intubation	37/39 (95%)	8/9 (89%)	29/30 (97%)

Table 2
Clinical course of patients admitted over the 2 time periods.

	All patients	2012 patients	2017 patients	p*
ICU LOS days	n = 41	n = 9	n = 32	
Median (IQR)	4 (3–10)	2 (2–3)	7 (3–13.5)	0.001
HCU LOS days	n = 39	n = 9	n = 30	
Median (IQR)	1 (0–2)	0 (0–0)	1 (0–2)	0.050
Total LOS days	n = 38	n = 9	n = 29	
Median (IQR)	5 (3–15)	2 (2–3)	8 (4–17)	0.000
Antidote days	n = 35	n = 7	n = 28	
Median (IQR)	4 (2–9)	2 (2–3)	5 (3–10)	0.004
Ventilator days	n = 37	n = 7	n = 30	
Median (IQR)	3 (1–8)	1 (1–2)	4 (2–11)	0.003

* p value for Mann Whitney U test.

Table 3
Complications (Cx) observed over the 2 time periods.

	All patients	2012	2017	p[a]
Documented Cx	44% (18/41)	33% (3/9)	47% (15/32)	0.47
AB No	78% (29/37)	71% (5/7)	80% (24/30)	0.62
Re-intubation	20% (7/35)	0% (0/7)	25% (7/28)	0.3
Tracheostomy	18% (7/39)	0% (0/9)	23% (7/30)	0.17
Inotrope use	10% (4/39)	0% (0/9)	13% (4/30)	0.56

[a] X^2 test/Fisher exact test.

Discussion

This study has confirmed our suspicion that while there were some similarities between our two cohorts of patients, the presentation of OPP between 2012 and 2017 has evolved. Given the more severe clinical presentation in 2017, it is possible that several cases seen in 2012 were in fact carbamate poisoning with aldicarb and not true OPP.

The choice of the periods of investigation requires some discussion. A phased withdrawal was announced by the manufacturer during 2011 and there was already knowledge that products sold in neighbouring countries would find their way into South Africa [28]. This meant that effectively an alternative product would likely only become established over an extended period. We therefore wanted two periods that were chronologically far enough apart (washout period) that the clinical changes were clearly demonstrable. In addition, this needed to be balanced by the periods being close enough that changes and advances in care would not present a significant bias. We used this as our rationale for choosing to look for differences between 2012 and 2017. The periods were appropriately chosen to meet our primary objective.

The main finding of our study was that the LOS in ICU was significantly longer in 2017 than in 2012. In comparison, other international studies have reported mean ICU lengths of stay between 0.6 days and 3 weeks [12–15]. This wide variability in LOS throughout the world is probably related to the different chemical composition of organophosphates available and the inclusion of carbamate poisoning.

LOS is directly proportional to cost. Both the cost per patient and total annual cost of OPP admissions were several times higher in 2017 compared to 2012. The total ICU cost in 2017 was 31 times higher in 2017 compared to 2012. Using 2016 adjusted costs, the total cost in 2012 was just under ZAR 500,000 (USD ~35,000) compared to ZAR 15 500,000 (USD 1,100,000) in 2017. The average cost per admission in 2017 was approximately ZAR 189,000 (USD 13,800), over three times the average cost per patients in 2012 which was ZAR 54,000 (4000 USD). In comparison, a study from 2005, performed in Sri Lanka, reported the highest treatment cost for a single patient with OPP as 308.86 USD [16]. This highlights how variable the cost of health care is throughout the world, and particularly the high cost burden of OPP in South Africa. It may also reflect the setting in which patients are managed e.g. Intensive Care Unit or high dependency unit vs. ward.

The shortage of critical care resources in South Africa is a well-known problem described previously [17]. A South African ICU not dissimilar to our study showed that 12.6% of patient refusal of admission to ICU was due to lack of bed availability [18]. Delayed ICU admission or care for critically ill patients outside the ICU due to lack of resources results in poor outcomes. [19,20] The African Surgical Outcome Study (ASOS) study revealed that, while African patients requiring emergency surgery are younger, have a lower risk profile and lower complications, they are more likely to die partly due to limited access to critical care services [21]. Based on the excess ICU cost in 2017 compared to 2012, in real terms, we have lost 557 ICU patient days. This is what we stand to gain if we find a therapeutic strategy to shorten the

Table 4
Comparison of ICU cost of OPP cases between 2012 and 2017.

	2012	2017	Increase
ICU median LOS days	2	7	2.5 fold
ICU admission	9	32	2.6 fold
Cost per patient	ZAR 54000.00	ZAR 189000.00	2.5 fold
Cost per year	ZAR 486000.00	ZAR 15552000.00	31 fold

All costs are priced at 2016 South African Rand prices (R27 000 per day in ICU).

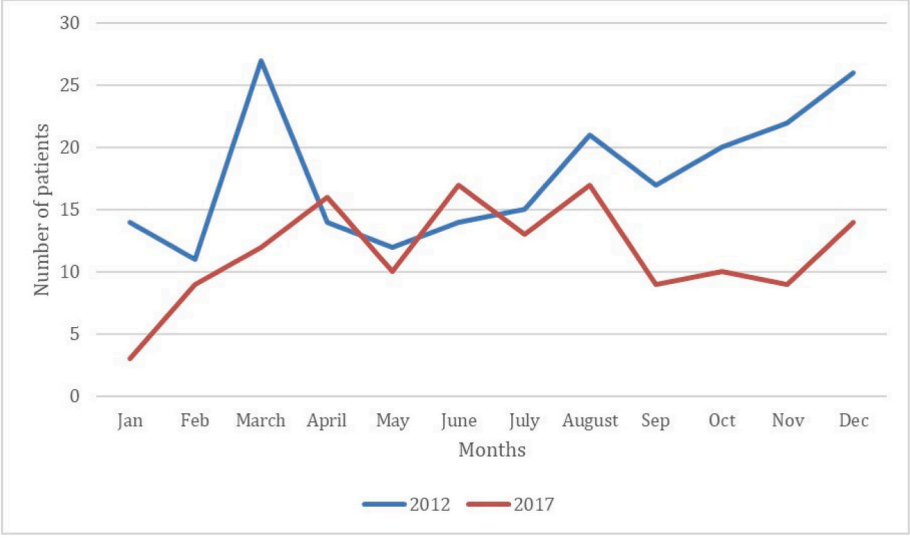

Fig. 1. Number of patients presenting to the Emergency Department with OPP.

disease course to that previously found in 2012.

With respect to the difference in complication rates between the 2 periods, it was not possible to show statistical significance. Re-intubation, vasopressor use and tracheostomy requirements were non-existent in 2012 and they increased to between 13% and 25% in 2017, while ICU utilization increased over 5-fold in 2017. There is little doubt regarding the clinical significance of the increase in these complication rates among patients in the 2017 cohort when compared to 2012. This, together with the increased need for ICU in 2017, supports the idea of an increase in severity of disease in 2017 compared to 2012. It is plausible that this may reflect a change in the culprit toxin between the 2 time periods; a carbamate with a milder disease course in 2012 compared to an organophosphate with a more severe clinical course in 2017.

With regards to mortality, there were no deaths in ICU in 2012 while we observed a mortality rate of 10% in 2017. In comparison, previously published data reported a case fatality rate of 3.7% locally [4]. However, it is important to point out that our sample population consisted of only critically ill patients admitted to the ICU and therefore excluded milder cases treated in the medical wards. Internationally, the mortality rates secondary to OPP range between 4% and 50% [22–25]. Our results from 2017 are in keeping with the results of Hussain et al. who reported a mortality rate of 8% in ventilated patients [26].

Our data showed a male predominance in both time periods which is in keeping with international data [12,27,28]. The mean age of presentation was also similar to international data, which was 29 years of age in 2012 and 30,5 years of age in 2017 [28].

All patients involved in the study had intentional OPP. This was substantially higher than the figure of 52% previously quoted by Razwiedani & Rautenbach in another South African study [4]. However, other international studies have reported similar rates of intentional OPP, between 68 and 96% [26,29–32]. In contrast to international data which demonstrated that OPP is more common in summer holidays, an association attributable to the use of organophosphate in agriculture, we observed peaks in OPP cases in 2012 in March, August and December, and in April, June, August and December in 2017. These months do not correspond to a specific weather pattern in South Africa. This discrepancy could be easily explained by the following. Most of our cases were intentional OPP and secondly, Johannesburg is a not an agricultural area. Of interest, these periods do fall within national school and tertiary institution holiday periods.

Organophosphate poisoning in South Africa has been a public health problem for decades. In 2011 the initial steps were taken to withdraw aldicarb, nicknamed “two-steps” from store shelves in South Africa. This was the beginning of the phasing out process [33]. This informal name, “two-steps” refers to the number of steps that rodents can supposedly take before dying following ingestion [34]. It is likely that people living in informal settlements and those with poor municipal services use these compounds to effectively control pests. This phasing out may have contributed to the market for a replacement of the withdrawn product. Among these replacements is terbufos an organophosphate compound, which is illegally decanted and sold on the streets in unlabeled containers [35]. It can be expected that as long as poor infrastructure and poor service delivery prevails, the demand (and therefore the availability) of these hazardous products will remain.

This change in clinical presentation in recent times has not been documented in the South African literature and is of great public health significance. Previous authors have noted the problem of pesticide exposure and the weakness in the current notification system [4,35]. In 2012, Rother HA suggested the need for strengthening of our local surveillance systems but given our current findings several years later, it appears that this problem still needs to be addressed. We would like to suggest that the urgency of this problem now requires a two-pronged approach; firstly re-emphasizing the public health issue and the failure to address it thus far and secondly we believe that the development of novel clinical strategies are urgently required to help deal with the disease burden.

This was a retrospective study in a large but single hospital. Patients that did not require ICU admission were excluded. This could be regarded as both a limitation and strength of this study. It seems intuitive to think that because of these exclusion criteria, our results might be underestimating the extent of the problem. However, this also meant that many cases of carbamate poisoning, which tend to be of milder severity and short-lived were essentially excluded. Another limitation is that the true cost of these cases might have been underestimated using an average cost as these patients are likely part of a group of resource intensive users e.g. special investigations such as CT scans, EEG and procedures such as tracheostomies.

Conclusion

Based on our experience, the clinical course of OPP requiring ICU admission has evolved into a condition with a longer length of stay, duration of antidote therapy, ventilatory support, increased risk of complications and additional costs.

CRediT authorship contribution statement

All authors contributed to the design and approach of the paper, literature review and analysis, article drafting, final approval and submission.

Dissemination of results

Results were informally disseminated to the members of the ICU department. Results were also discussed with the Emergency Centre of the hospital.

Authors’ contribution

Authors contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: SO contributed 50%; IAB 20%; LT and KMSP contributed 12.5%; and AK contributed 5%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Availability of data and materials

Anonymous raw data is available on request.

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Declaration of competing interest

The authors declared no competing interests.

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