PRESENTATION AND OUTCOMES OF CHILDREN ADMITTED WITH ORGANOPHOSPHATE AND CARBAMATE POISONING AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Paediatrics.

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DECLARATION

I, Sibongile Dlamini declare that the research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

3 October 2023

I, certify that the study contained in this thesis has the approval of the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg. The ethics clearance number is M190126.

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3 October 2023

DEDICATION

To my loving husband Kgosietsile Tlalang, for his constant support.

And to my beautiful daughters Tshimologo and Tswelelopele for their patience.

ABSTRACT

BACKGROUND:

Children are a vulnerable population for organophosphate and carbamate poisoning (OP/CBM). The World Health Organization reports mortality up to 10%. These agents then cause muscarinic, nicotinic and central nervous system collapse.

OBJECTIVES:

To describe the demographics and clinical features of OP/CBM poisoning, document the treatment given and the response thereof. Observe the acetylcholinesterase levels in relation to clinical features and assess outcomes of the participants.

METHODS:

A retrospective cross-sectional record review of patients (<14 years) presenting with OP/CBM poisoning at Rahima Moosa Mother and Child Hospital (RMMCH) from the 1st of February 2016 to the 31st of March 2018. Demographics, poisoning circumstances, clinical features, investigations, management and outcomes were analysed.

RESULTS:

Over the two-year period, 28 participants were included in the study. Gender distribution was equal, and the median age was 31,5 months (Interquartile range [IQR]: 17.5-32.0). Majority was due to accidental poisoning (85%). On arrival to RMMCH, 42.9% were unconscious, displaying mostly Nicotinic (85.7%) vs Muscarinic (71.4%) symptoms. All the participants received Atropine as part of their initial treatment. Participants that had poor outcomes (i.e., demised, n=6/28, 4.7%) were more likely to require inotropes (p=0.02), suffer seizures (p=0.003) and have metabolic acidosis (p=0.02).

CONCLUSION:

OP/CBM poisoning can have devastating outcomes. Improvement on trade, storage and legislation of these agents is of importance. Research on long-term effects of poisoning would be beneficial.

ACKNOWLEDGEMENTS

A special thanks to my supervisor Dr Tim De Maayer and my mentor Professor Sithembiso Velaphi who provided guidance and encouragement throughout.

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ABBREVIATIONS

OP:	Organophosphate
CBM:	Carbamate
CNS:	Central Nervous System
SLUDGE:	Salivation, Lacrimation, Urination, Defecation, Gastrointestinal cramps, Emesis
STG:	Standard Treatment guidelines
RMMCH:	Rahima Moosa Mother and Child Hospital
SA:	South Africa
MO:	Medical officer
REDCAP:	Research Electronic Data Capture
IQR:	Interquartile range
HIV:	Human Immunodeficiency Virus
E. coli:	Escherichia coli
RDP:	Reconstruction and Development Program
pGCS:	paediatric Glasgow Coma Score
PICU:	Paediatric Intensive Care Unit
PPV:	Positive Pressure Ventilation
ARDS:	Acute Respiratory Distress Syndrome
RCC:	Red Cell Cholinesterase
pChE:	Plasma Cholinesterase
BBB:	Blood Brain Barrier

SUBMISSIBLE PAPER

PRESENTATION AND OUTCOMES OF CHILDREN ADMITTED WITH ORGANOPHOSPHATE AND CARBAMATE POISONING AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

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Key words

Organophosphate

Carbamate

Intoxication

Acetylcholinesterase

1. INTRODUCTION

In the emergency department, healthcare workers are regularly challenged with poisoning in the paediatric patient. Hydrocarbons and pesticides remain the leading poisonous agents identified (1).

Pesticides are used frequently in agriculture, industry and in the domestic setting. Organophosphate (OP) and carbamate (CBM) are examples of pesticides that are readily available, and as a result intoxication (intention or accidental) is not infrequent, especially in developing countries. According to the World Health Organization, mortality due to pesticide poisoning, in adults is between 22-25%, while in the paediatric population mortality has been documented just below 10% (2).

Accidental oral ingestion of OP/CBM is most common in children under five years, while self-harm is more common in older children and adults (3). Route of exposure, timing of presentation to health care and duration of exposure affect the expression of the clinical features manifested (3, 4). Specific receptors that affected by OP/CBM poisoning are muscarinic and nicotinic. The OP action is at the level of the neuromuscular junction of the nervous system (peripheral and central), where it inactivates acetylcholinesterase. This leads to accumulation of acetylcholine resulting in over stimulation of the nicotinic and muscarinic receptors (4).

Muscarinic symptoms include Salivation, Lacrimation, Urination, Defecation, Gastrointestinal cramps, and Emesis. These symptoms for the acronym SLUDGE. While the nicotinic symptoms are results of the motor and the sympathetic nervous systems being affected. They are tachycardia, hypertension, fasciculations and muscle weakness (4).

Prolonged or delayed features, such as extrapyramidal symptoms, have been documented which have been associated with poor outcomes. Some co-morbidities have also been linked in prolonged symptoms such as malnutrition, congenital and acquired heart disease, liver conditions and renal (5).

The management of a patient with OP/CBM poisoning is includes the clinician's ability to recognize the clinical features, followed by adequate decontamination, resuscitation and administration of the Atropine and oximes. Severe cases my require the use of mechanical ventilation and inotropes (6, 7). Atropine, an anti-muscurinic, which penetrates the Central

Nervous System (CNS) (7). Atropine's major CNS side effect is delirium, and patients need to be monitored closely if this occurs. Atropine is also known for its anti-cholinergic adverse events i.e., blurred vision, dry mouth, constipation, and urinary retention, only to name a few (8). Glycopyrrolate can be used as an alternative to Atropine as it does not penetrate the CNS. In South Africa, Atropine is recommended treatment for OP/CBM as per the national Standard Treatment guidelines (STG). It is cost effective and readily available (5, 9). The use of oximes such as Pralidoxime and Obidoxime has shown to be favourable (safe for use on children, reducing need of intubation and mortality rates) in other countries around the world (10, 11). Oxime's mechanism of action is through reactivation of acetylcholinesterase and are most effect when used in the first 48 hours of presentation. (11). Research on it's vasopressive effects are still underway, as a common complication is hypotension from OP/CBM poisoning which causes cardiotoxicity (12).

Poor outcomes such as cardio-respiratory collapse, have been documented to be related to prolonged exposure and delay in decontamination (13).

South Africa, like many other developing countries, are having challenges with surveillance and victims of OP/CBM poisoning. There is minimal data that entirely focused on the paediatric pesticide poisoning. One study of note; is one conducted in the city of Tshwane, in Gauteng, South Africa, projecting a third of the population in the study were children, but the study's emphasis is on the adult group. It is therefore essential to document OP/CBM poisoning children in South Africa (14).

2. METHODS

Study design

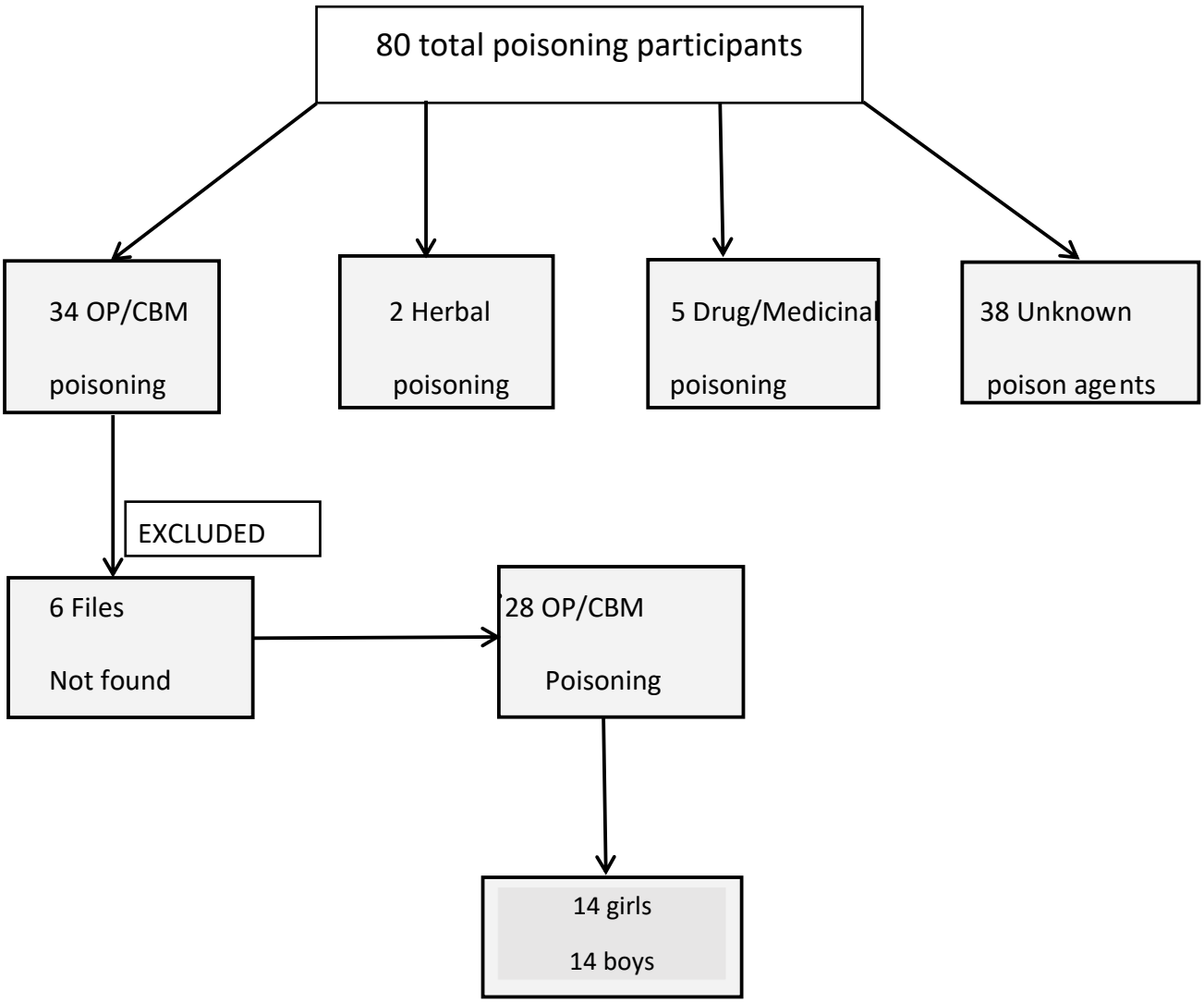
This was a retrospective, descriptive study of children (0-13 years) at Rahima Moosa Mother and Child Hospital (RMMCH) admitted for OP/CBM poisoning from the 1st of February 2016 to the 31st of March 2018. RMMCH is a secondary level, academic hospital in Coronationville, Johannesburg in South Africa (SA). It is a referral center for surrounding local clinics, community health care centers, and hospitals.

The diagnosis of OP/CBM poisoning was made on history and clinical features.

Study population

All patients admitted with OP/CBM poisoning were included. Patients whose files could not be found, and those who had poisoning from agents other than OP/CBM were excluded from the study.

Figure 1: Participants included in the study of presentation and outcomes of children with organophosphate and carbamate poisoning at RMMCH from 1 February 2016 – 31 March 2018



Data collection

Patient data was collected from two sources:

1. File numbers of patients admitted with poisoning in the pre-defined time period were identified using the REDCap database – a web-based electronic database hosted by the university of the Witwatersrand capturing basic admission data.

2. Hospital file – which was found on the hospital premises is in the filing room.

Data captured included demographics, caregiver details, details of the poison (if available), clinical features on arrival, admission details, management, and outcomes.

Statistical analysis

Data was analysed using STATA 15.0 (Stata Corp, 4905 Lakeway Drive, College Station. Texas, 77845 USA). Categorical variables were used to describe the findings, using frequencies and percentages. Continuous variables were described using medians (with interquartile range [IQR]) as data was non-parametric. Correlations between variables were assessed using Fisher's exact test as cell sizes were small. P- value of <0.05 is statistically significant.

Ethics

Approval of the study is from The Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa. Clearance certificate number M190126. (See annexure list.)

3. RESULTS

Characteristics

A total of 34 participants were documented to have OP/CMB poisoning but 6 were excluded due to incomplete records. The median age of the remaining 28 participants was 31.5 months (Interquartile range [IQR]: 17.5 – 32.0), gender distribution was equal, and apart from one child with eczema, none were known to have any chronic diseases at the time of presentation. The majority of the OP/CBM was obtained at an informal market

(64%), not correctly labelled (57%), and participants largely ingested poison accidentally (85%). The average age of those with accidental exposure (34.2 months, IQR: 19.6 – 42.5) did not differ significantly from those exposed through attempted homicide (17.8 months, IQR: 10.3 – 28.4) (Wilcoxon rank-sum test p= 0.12). The oldest child in the cohort was 12 years and was exposed during an attempted suicide.

Table 1: Demographics characteristics of patients presenting with OP/CBM poisoning

Description	**n (%) or Median (IQR, Range)**
Age (Months)	31.5 (17.5 – 42, 9.1 – 151.4)
Male	14 (50.0)
Female	14 (50.0)
HIV positive	1 (3.6)
Weight (kg)	13.2 (10.8 - 18.0, 8.0 – 43.0)
Height (cm)	82 (79 - 92, 72 - 143)
Caregiver	
Mother	21 (75.0)
Father	1 (3.6)
Grandparent	3 (10.7)
Other	2 (7.1)
Unknown	1 (3.6)
Caregiver's level of education	
None	2 (7.1)
Primary	2 (7.1)
High	7 (25.0)
University	1 (3.6)
Unknown	16 (57.1)
Type of housing	
Informal	3 (10.7)
RDP*	8 (28.6)
Flat/House	10 (35.7)
Unknown	7 (25.0)
Source of OP/CBM	

Formal	3 (10.7)
Informal	18 (64.3)
Unknown	7 (25.0)
Labelling of OP	
Labelled	4 (14.3)
Unlabeled	16 (57.1)
Unknown	8 (28.6)
Circumstance	
Accidental	24 (85.7)
Parasuicide	1 (3.6)
Homicide	3 (10.7)
Route of exposure	
Ingestion	28 (100.0)

RDP: Reconstruction and Development Program

Clinical features (See Table 2)

The characteristics of the patients are well described in Tables 2. Five of the patients had comorbidities, including two with a lower respiratory tract infection, one with an *Escherichia* coli (E. coli) urinary tract infection, the one with dysentery and lastly one with newly diagnosed with HIV infection.

The time to initial treatment of the patients after exposure was an average of four hours with more than 40% of the participants arriving unconscious, according to the paediatric Glasgow Coma Score (pGCS) of between 3 and 5 (14). Nicotinic symptoms and muscarinic symptoms occurred in 85.7% and 71.4% respectively. Three patients were transferred out to other paediatric intensive care units (PICU).

All patients initially received atropine. As an alternative, Glycopyrrolate was used as an anti-cholinergic in three patients, as they developed atropinergic central nervous system side effects. Eleven patients had Acetylcholinesterase tested, but tests used differed according to availability (in stock or not at the laboratory); either Red Cell Cholinesterase (RCC) or Plasma Cholinesterase (pChE). Third generation cephalosporins were given to 11 (39.3%) patients, mostly in those who presented with a decreased level of consciousness.

Table 2: Clinical features of patients presenting with OP/CBM poisoning

Description	n (%) or Median (IQR, Range)
Median Time between exposure and initial treatment in hours	4
Comorbidities (n=5)	
Pneumonia	2 (22.2)
HIV	1 (11.1)
Dysentery	1 (11.1)
E. coli UTI	1 (11.1)
Level of consciousness	
Alert n (%)	6 (21.4)
Verbal n (%)	9 (32.1)
Pain n (%)	1 (3.6)
Unconscious n (%)	12 (42.9)
Nicotinic symptoms n (%)	24 (85.7)
Tachycardia n (%)	23 (82.1)
Hypertension n (%)	10 (35.7)
Metabolic acidosis n (%)	11 (39.3)
Skeletal muscle weakness n (%)	13 (46.4)
Fasciculations n (%)	1 (3.5)
Paralysis n (%)	3 (10.7)
Muscarinic symptoms n (%)	20 (71.4)
Pupil constriction n (%)	24 (85.7)
Bronchospasm n (%)	13 (46.4)
Lacrimal secretions n (%)	3 (10.7)
Nasal secretions n (%)	6 (21.4)
Sweating	3 (10.7)
Bronchial secretions n (%)	17 (60.7)
Bradycardia	2 (7.1)
Shock	5 (17.9)
Diarrhoea	5 (17.9)

Ache Level	15 (53.6)
Red Cell Cholinesterase	5 (540-7776) N:4528-7056
Pseudocholinesterase	6 (104-9405) N:4620-11500
Sample Rejected	4 (26.7)
Area of admission on arrival	
Paediatric ward	8 (28.6)
RMMCH ICU	19 (67.9)
Transfer to external ICU	1 (3.5)
Highest level of respiratory support	
Nasal Prong 0_2 n (%)	3 (10.7)
Face mask n (%)	1 (3.6)
PPV n (%)	20 (71.4)
Room air n (%)	4 (14.3)
Treatment	
Atropine n (%)	28 (100)
Glycopyrrolate n (%)	4 (14.3)
Inotropes n (%)	4 (14.3)
Ceftriaxone	12 (41%)
Complications	
Arrhythmia n (%)	1 (3.5)
Seizures n (%)	8 (28.6)
Respiratory failure n (%)	8 (28.6)
Outcomes	
Discharged n (%)	19 (67.9)
Transferred n (%)	3 (10.7)
Death prior to hospital discharge n (%)	6 (21.4)

*E. coli: Escherichia coli

*UTI: Urinary Tract Infection

*PPV: Positive Pressure Ventilation

Outcomes (see Table 2 and 3)

Six children presenting with OP/CBM poisoning died during their stay from the poisoning and its complications. Most (67%) of the patients were discharged, while three were transferred out (all three survived). Factors associated with poor outcome were the use of vasopressive agents e.g. Dopamine and inotropic agents e.g. Dobutamine (p= 0.02). These agents were used either due to hypotension or cardiogenic shock. The presence of seizures also lead to unfavorable outcomes (p= 0.003).

Table 3: Factors associated with outcome.

Variable	**Overall (n= 28)**	**Alive (n= 22)**	**Dead (n= 6)**	**p-value***
HIV positive n (%)	1 (3.6)	0 (0)	1 (16.7%)	0.21
Median age in months (IQR)	31.5 (17.5 – 42)	31.5 (18 – 46)	29.5 (12 – 37)	0.40
Median weight in kg (IQR)	12.85 (10.8 – 16)	12.85 (11 – 18)	13.5 (8.4 – 15)	0.39
Median length of stay in days (IQR)	1 (2 – 5)	2.5 (1 – 6)	1 (1 – 3)	0.12
Decreased level of consciousness n (%)	22 (78.6)	16 (72.7)	6 (100)	0.29
Intermittent positive pressure ventilation n (%)	20 (71.4)	14 (63.4)	6(100)	0.14
Drugs				
Atropine n (%)	28 (100)	22 (100)	6 (100)	N/A
Glycopyrrolate n (%)	4 (14.3)	3 (13.6)	1 (16.7)	0.64
Inotropes n (%)	4 (14.3)	1 (4.6)	3 (50.0)	**0.02**
Ceftriaxone n (%)	11 (39.3)	7 (31.8)	4 (66.7)	0.17
Complications				
Arrhythmia n (%)	1 (3.6)	0 (0)	1 (16.7)	0.21
Seizures n (%)	8 (28.6)	3 (13.6)	5 (83.3)	**0.003**
Respiratory Failure n (%)	4 (14.3)	3 (13.6)	1(16.7)	0.64
Serum lactate (IQR)	2.6 (1.6 – 7.1)	2.4 (2.1 – 3.1)	5.3 (1.6 – 13.8)	0.19
Metabolic acidosis (HCO3- < 20)	16 (57.4)	10 (45.5)	6 (100)	**0.02**

*P-values obtained from the Fisher's exact test. p<0.05

Percentages as from column total

4. DISCUSSION

OP/CBM poisoning is still a global issue and especially challenging in the developing countries such as South Africa (6). This study showed almost a third of poisoning presenting to RMMCH were OP/CBM poisoning. The route of exposure for all participants was oral, and more than 85% was accidental. A younger population are prone to accidental exposure whether oral or inhalation, depending on the setting, i.e urban or rural (11, 13).

Six patients demised, giving a mortality rate of 21.4%. The age range of the patients in the study (1.4 - 12 years). More than half of the participants stay in formal housing, which is contrary to Balme et al, who associated is an increase in pests due to crowed unhygienic living spaces, resulting in informal "street pesticide" sales of OP/CBM (14).

In this study most caregivers to the participants are their mothers (75%), living in the peri-urban and urban areas of Johannesburg. The level of education of the caregivers was only documented 43% of and only four caregivers did not proceed beyond primary school. Incorrectly and unlabeled packaging in this study was together as high as 75%. In another study in South Africa, noted that women in urban and peri-urban areas live in poverty and overcrowded areas which leads to pests and increased use of pesticides that are low cost (obtained from informal markets) and packaged and labelled inappropriately (15).

Table 2 describes the clinical features of the participants. The arrival of the participants to hospital was at a median of four hours, which according to Yousef et al, is associated with poor outcomes, i.e. higher lactate levels, Acute Respiratory Distress Syndrome (ARDS) and ultimately higher mortality rate (16). Nicotinic symptoms were more common (85.7 %) than Muscarinic symptoms (71.4 %). The muscarinic symptoms respond well Atropine, which all participants in the study received. Glycopyrrolate was used if participants had side effects secondary to atropine e.g., Hallucinations and delirium. While nicotinic symptoms are said to respond better to oximes e.g., Pradolixime, if given within the first 48 hours to function optimally and reverse the effects of the OP (16). However, oximes were not available in our setting. Acetylcholinesterase (Ache) levels were done in just over half of the participants. Some results of the RCC & PCHe were within the normal ranges, even though the participants were clinically symptomatic. At times there were delays in the time the blood sample taken (drawn from patient) and the time in which the blood sample processed. This finding can be explained in a few ways: baseline (prior to poisoning) levels of Ache are

variable, and those with a higher baseline may not reach the deficiency cutoff, according to Wiener & Hoffman (17, 18). Other studies alluded to the dosage of the poisoning, route of exposure and rate of absorption affect levels (19). In our study, the time between admission and taking the Ache samples was unfortunately not documented. Storage and transport of the blood to be analysed for OP/CBM poisoning should not be at room temperature as it would cause reactivation of the poisonous agent (20).

Table 3 compares the participants that survived versus those who demised as a complication from OP/CBM poisoning. In this study, the use of inotropic agents(p=0.02), presence of seizures (p=0.003) and the presence of metabolic acidosis (p=0.02) were associated with death. Although elevated lactate was previously identified as a poor prognostic marker, it did not reach significance in this study (16). The need for inotropic agents (Dopamine and Dobutamine) likely represents patients with more severe illness. Hypotension is described by Davis et al is due to a combination of cardiotoxicity, peripheral vasodilatation leading to distributive shock in patients with OP/CBM poisoning (18). In another study, conducted in Nepal, which included both children and adults, showed that a fewer younger patients had low blood pressures and required inotropes (19). In the current study seizures were a common complication and were associated with mortality (83.3% vs 13.6%, p= 0.003). The neurotoxicity caused by the OP/CBM poisoning results in an altered sensorium and increase neuro-electrical activity which may lead to seizures. Tonic-clonic seizures are said to be more common in the younger population. The initial seizure may also predispose to subsequent seizures in the future (17, 20).

Malnutrition is one of the conditions contributing to a lowered activity of cholinesterase and is also associated with severity of OP/CBM poisoning (6, 16). Assessment of nutrition in this study could only be done in 17 (60%) of the participants, due to inadequate data captured in the admission files. Fourteen of these (82.4%) had a normal weight for height or body mass index (BMI) for age, while two had moderate acute malnutrition (Weight for height <-2) and one severe acute malnutrition (weight for height < -3). Sub-optimal nutrition has previously been linked with poor outcomes in OP/CBM poisoning, however none of the three children with acute malnutrition had adverse outcomes. One underweight participant (weight for age < -2) was newly diagnosed HIV positive (Antiretroviral naive) and demised.

Four patients that were treated with glycopyrrolate after suffering side effects of atropine. While both are anticholinergic agents, atropine can cross the Blood Brain Barrier (BBB). This comes to be an advantage of effected (alleviates CNS Symptoms) but also a culprit for CNS side effects and toxicity (11, 14, 22). Cardiac complications, such as arrhythmias, from OP/CBM poison is common occurrence and leading to death but was only documented in one of our patients (23).

5. STUDY LIMITATIONS

Due to the retrospective nature of the study, it was reliant on retrieving data from the files or REDCap. Difficulty in finding files and the limited information written about the participants led to exclusion of some participants, and missing data for others. A small sample size. Follow up of participants to assess prolonged symptoms was not possible / documented. AChe levels were not always taken at the time of admission, and some were delayed in transportation and subsequently rejected. Serial measurements of Ache were not performed.

6. CONCLUSION

Children presenting with OP/CBM poisoning in this study had a median age younger than 3 years and were all due to accidental ingestion. Participants presented mostly with nicotinic symptoms and only about half of them had Acetylcholinesterase levels done. All the participants were treated with Atropine as first line treatment. Those that needed inotropic support had unfavourable outcomes. Complications that lead to death included arrythmias, seizures, respiratory failure and metabolic acidosis.

Improvement in legislation, trade, storage of these pesticides would assist in curbing the high burden of morbidity and mortality due to OP/CBM poisoning.

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8. APPENDICES

1. MMED PROTOCOL

Title: Presentation and outcomes of children admitted with organophosphate and carbamate poisoning at Rahima Moosa Mother and Child Hospital

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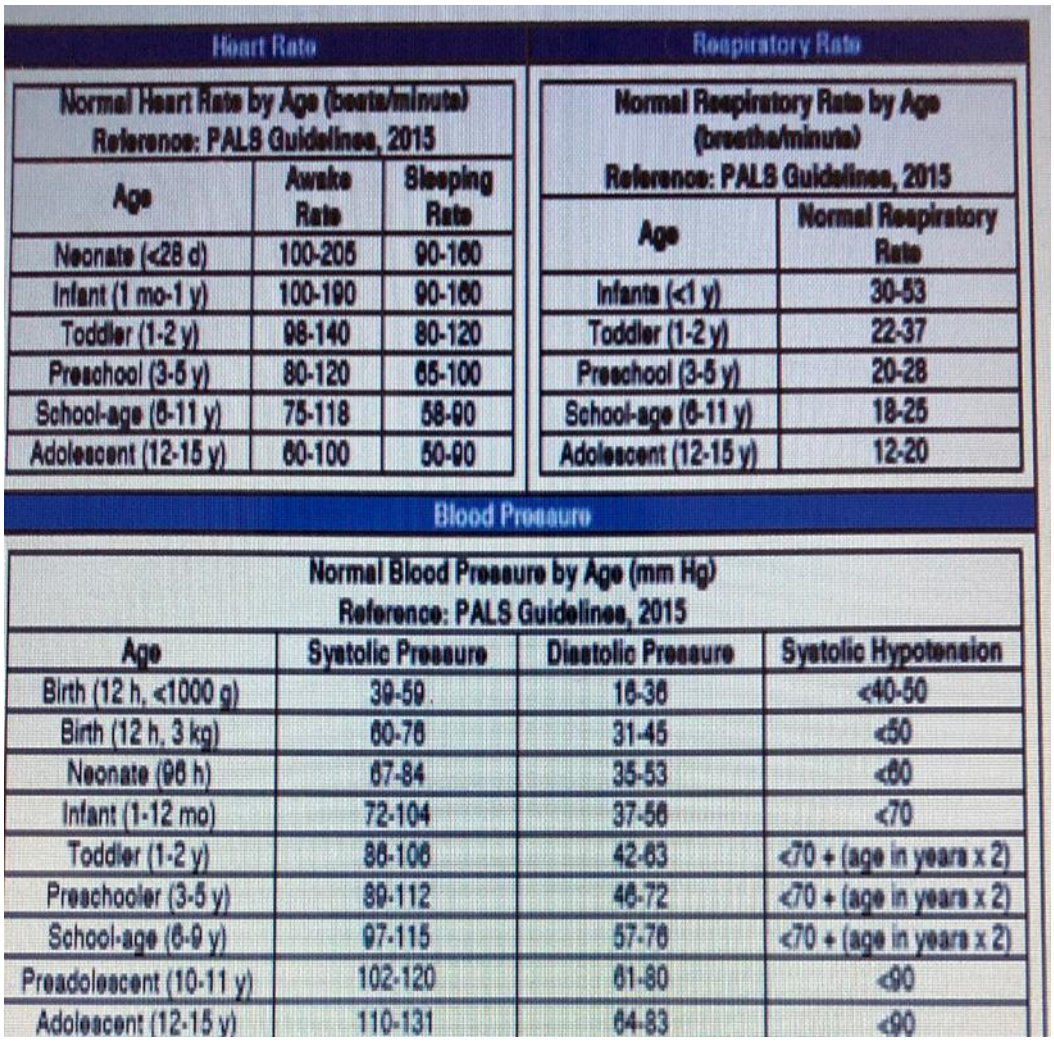
INDEX

I. GLOSSARY

OP	Organophosphates
CBM	Carbamates
ACh	Acetylcholine
AChE	Acetylcholinesterase
RMMCH	Rahima Moosa Mother and Child Hospital
Paediatric patient	Age: 0-13yrs
REDCap	Research Electronic Data Capture
CNS	Central Nervous System
RBC	Red Blood Cell
FBC	Full Blood Count
WCC	White Cell Count
Hb	Haemoglobin
U&E	Urea and Electrolytes
Na	Sodium
K	Potassium

Cl	Chloride
HCO3	Bicarbonate
Ur	Urea
Creat	Creatinine

II. VITALS: NORMAL RANGES



Heart Rate

Normal Heart Rate by Age (beats/minute)
Reference: PALS Guidelines, 2015

Age	Awake Rate	Sleeping Rate
Neonate (<28 d)	100-205	90-160
Infant (1 mo-1 y)	100-190	90-160
Toddler (1-2 y)	98-140	80-120
Preschool (3-5 y)	80-120	65-100
School-age (6-11 y)	75-118	58-90
Adolescent (12-15 y)	60-100	50-90

Respiratory Rate

Normal Respiratory Rate by Age (breaths/minute)
Reference: PALS Guidelines, 2015

Age	Normal Respiratory Rate
Infants (<1 y)	30-53
Toddler (1-2 y)	22-37
Preschool (3-5 y)	20-28
School-age (6-11 y)	18-25
Adolescent (12-15 y)	12-20

Blood Pressure

Normal Blood Pressure by Age (mm Hg)
Reference: PALS Guidelines, 2015

Age	Systolic Pressure	Diastolic Pressure	Systolic Hypotension
Birth (12 h, <1000 g)	39-59	16-36	<40-50
Birth (12 h, 3 kg)	60-76	31-45	<50
Neonate (96 h)	67-84	35-53	<60
Infant (1-12 mo)	72-104	37-56	<70
Toddler (1-2 y)	86-106	42-63	<70 + (age in years x 2)
Preschooler (3-5 y)	89-112	46-72	<70 + (age in years x 2)
School-age (6-9 y)	97-115	57-76	<70 + (age in years x 2)
Preadolescent (10-11 y)	102-120	61-80	<90
Adolescent (12-15 y)	110-131	64-83	<90

III. LITERATURE REVIEW

1. Introduction

Poisoning has become an increasing cause of morbidity and mortality worldwide. The agents causing this vary from household, medicinal (modern /traditional), pesticides, plants, food and illicit drugs. [1]

Pesticides are agents that describe a vast group of chemicals whose sole function is to eliminate plants(herbicides), insects(insecticide), rodents(rodenticide) & moulds (fungicide). Exposure to these agents acutely or chronic contact may result in toxic effects. [2]

In South Africa a study reported 200 000-300 000 cases of accidental poisoning annually. Kerosene(paraffin) is still the most common poisonous agent in the paediatric population, followed by medicinal agents. What is on an upward trend is organophosphate (OP), carbamates (CBM), paracetamol and corrosive agents. [3]

Accessibility of pesticides has become easy. Street pesticides (mainly against cockroaches and rodents) is a market that is on the rise in South African 17% of all admission and of that 36% are OP & CBM. Globally the trend seems to be similar, in the USA for example 45% of pesticide poisoning were children. In other developing countries such as India and Zimbabwe (20.9% and 62% respectively). The source of data regarding the extent of the problem is based on notification of these cases at healthcare facilities, poison call centers and research studies. Various formulations and combinations of these pesticides have been seen and packaged informally or inappropriately making the vulnerable population (i.e., children) at risk of accidental ingestion. [4, 12, 17]

Acetylcholine (ACh) a neurotransmitter which transmits impulses in the brain is affected when there is OP/CBM poisoning. It is found in the pre- and post-ganglionic fibers of the parasympathetic and sympathetic nervous system and in the skeletal muscles axon terminals. Once the (ACh) is released, it either inhibit or excite at different receptors sites (Muscarinic/Nicotinic/Central). In the skeletal muscle Ach causes contraction in various systems. ACh is rapidly catalyzed by Acetylcholinesterase (AChE) at the neuromuscular junction, preventing overstimulation of the receptor site. [6]

Exposure to OP/CBM, either by direct skin contact, oral ingestion, inhalation or eye contact would result in a "cholinergic crisis" due to a disruption of the equilibrium between ACh and

AChE. Organophosphates (lipid-soluble) forms an irreversible covalent bond with AChE and inactivation of AChE. Carbamates on the other hand tend to form a weak reversable bond with AChE. Once the bond as been formed by, this would cause continuous stimulation on the receptor sites by Ach and result in multisystem neurotransmission effects. [5, 6, 7].

The clinical manifestation of toxicity of OP/CBM vary depending on route of contact, age, duration and the type of pesticide. One case study in the Middle East showed that infants, patients with immature/diseased livers, those with inhalation of organophosphates as route of contact were factors associated with higher toxicity. [6, 9]

The clinical effects of OP/CBM, in the acute setting, muscarinic signs and symptoms are a result of parasympathetic nervous system overstimulation, leading to excessive lacrimation, rhinorrhoea, salivation, bronchial secretion, bronchial spasm, bradycardia and miosis. Simultaneously the nicotinic receptors are also affected, causing overstimulation of the sympathetic nervous system causing tachycardia, elevated blood pressure, mydriasis and excessive sweating. In the CNS patient would have features such as irritability, confusion, coma and respiratory failure. While at the level of the neuromuscular junction in the skeletal muscles they would present with fasciculations, muscle weakness and even paralysis. [5, 6]

Subacute symptoms were noted in a case report where patients presented up to 18 days post exposure to OP. Symptoms included muscle pain and weakness (distal lower limb more affected) with abnormal gait and palpitations. In another study in Ecuador, conducted about 10 days after flower harvest time showed that children exposed to pesticides had transient neuro-behavioural changes. These changes included a decrease in the following attention, inhibition, visuospatial processing and sensorimotor areas. [9, 13]

Long term (chronic) manifestations of poisoning that have been documented are abnormal/disturbed growth, neuro-developmental effects, endocrine disturbances, asthma and childhood cancers. This would be either due to ongoing exposure to pesticides found in food, water or inhalation.[2]

The investigations conducted to confirm or support the diagnosis of OP/CBM is measuring the levels of AChE, which would be low. In the CNS and in red blood cell (RBC) acetylcholinesterase also known as red cell cholinesterase and in plasma, it is butyl

cholinesterase and either of the two could be tested (to confirm the diagnosis) at depending on the laboratory. [2, 5, 8, 16] Decreased AChE levels have shown not to correlated with the severity of the clinical features, complications or outcome.

The management of OP/CBM starts by first removing the toxin by decontamination i.e., removal of direct contact of toxin; clothing, washing skin and eyes with water, gastric lavage. Healthcare workers are required to use Personal Protective Equipment (PPE) during decontamination process as pesticides are easily absorbed via routes mentioned earlier. Induced emesis is contraindicated as it increases the risk of aspiration which may lead to chemical pneumonitis. Assessing the of level of consciousness, cardio-respiratory systems, urine output, presence of seizures is imperative and can be indicators of prognosis and outcome. The mainstay of treatment is still Atropine an anticholinergic. Its function is at the muscarinic receptors where it antagonises the effect of Ach by decreasing cholinergic effects of OP/CBM. An alternative anticholinergic is Glycopyrrolate which does not penetrate the blood-brain-barrier therefore no CNS effect as compared to Atropine. Glycopyrrolate does however have side effects like gastrointestinal reflux and muscle weakness side effects. Close monitoring of the patient is important until fully atropinized. Other treatment modalities like Oxides may be used to reactivate AChE in specifically for Carbamate poisoning. Supportive treatment may be indicated for example Benzodiazepines for control of seizures. [5, 7]

Prognostic factors vary depending on where the study was done. In 2000 a study from Cape Town showed that poor outcomes were associated with a younger the age at presentation, presentation in coma, respiratory failure and seizures. While the route of contamination, delayed decontamination and Pseudocholinesterase levels were not major contributory factors. An adult study (only 7 children) in Korea, in 2014, made the link of poor prognosis and obesity, arguing that due to the lipophilic nature of OP, patients that had higher Body Mass Index (BMI) had longer ICU stay and ventilation verses those with normal BMI. [15, 10]

The purpose of this study is to analyze the incidence and outcomes of children with pesticide poisoning at Rahima Moosa Mother and Child Hospital. There is a need to better understand the extent of the problem and therefore finding strategic solutions by prevention, appropriate early management and improve outcomes.

2. Aim

Presentation and outcomes of children presenting with organophosphate and carbamate poisoning at RMMCH from the 1st of February 2016 to the 30th of March 2018.

3. Objectives

a. Describe the demographics and clinical features of patients presenting with OP and CBM poisoning

b. To document the management and response to management implemented of patients presenting with OP and CBM poisoning.

c. Review whether RBC-AChE levels correlate with the severity of disease and outcome of patients with OP and CBM poisoning.

d. Analyze the outcome of the patients in review.

4. Methodology

a. Study Design

This will be a retrospective cross-sectional study, reviewing the medical records of patients presenting with Organophosphate and Carbamate poisoning at RMMCH from the 1st of February 2016 to the 31st of March 2018.

b. Sample Population

All paediatric patients presenting with Organophosphate and Carbamate poisoning at RMMCH, estimated 50-60 in the period stipulated above.

i. Inclusion Criteria

• All paediatric patients presenting with symptoms in keep with Organophosphate and Carbamate poisoning during the study period.

• Partly treated patients from other institutions referred to RMMCH

ii. Exclusion Criteria

• Incomplete or missing patient medical records.

• Patients age falling outside the paediatric age.

5. Data management and statistical analysis

Patient information from patient files and notification records will be recorded in Data Sheet. See APPENDIX A.

The information on the Data Sheet will be correlated with an already existing (at RMMCH) RED Cap database, which is a secure web application for building and managing online survey and databases. This database is updated on discharge of patient, all this date will be laid out on an Excel spread sheet.

The Data Sheet will include patient demographics, study number, circumstance of poisoning, clinical features, blood investigations, treatment, outcome etc.

Appropriate statistical analysis will be used to describe means and standard deviations or medians with interquartile ranges for continuous variables with skewed distribution. Comparisons will be done looking using Chi squared tests with Fisher's exact analysis to identify significant risk factors for adverse outcomes. Risk factors will be considered significant for p-value below 0.05. The statistical program for further analyses will be Statistica.

6. Outcomes

The study results and information obtained will be submitted towards MMED degree. Thereafter it will be shared as presentations and or publications. More importantly the results can be used to enlighten our communities, hospital management, government and policy makers in improving control, storage and preventing morbidity and mortality of Organophosphates and Carbamates.

7. Ethical considerations

As this is a retrospective study it will not be possible to obtain consent from the participants or their caregivers. The Data Capture Sheet will not contain any patient identifiers i.e., patient names, date of birth, addresses etc., there each patient will be given a unique number and be addressed as such.

The research will only commence once it has been reviewed by the Protocol Review Committee and Human Research Ethics Committee (HREC) at the University of the Witwatersrand. Permission will also be sought from the hospital's management.

8. Resources

Costs will be from purchasing of stationery, printing and binding which is estimated to be R500.00. All these costs will be met by myself, the Investigator.

9. Limitations

This being a retrospective study, the data collected will be dependent on the record keeping i.e., finding of the files, information documented and whether the patients were notified.

10. Time plan

1. TIME PLAN

	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MA
Review											
Protocol											
ıt											
plication											
ection											
ysis											
Proposal											
ın											

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2. DATA COLLECTION SHEET

DEMOGRAPHICS 1

Pt study number:

Age: Gender:

RVD Status:

Anthropometry:

Weight Height

Primary care giver:

1.Mother ○ 2. Father ○ 3. Grandparents ○ 4. ____

Other ○ Specify _____

Highest level of education of the caregiver:

1.None ○ 2. Primary School ○ 3. High School ○

4. Varsity ○

Type of residence:

1.Informal ○ 2. RDP house ○ 3. Flat/House ○

POISON DETAILS (if known)

Purchase: 1. Formal ○ 2. Informal/Street ○

Packing: 1. Labelled ○ 2. Unlabelled/ Incorrectly ○

Circumstance of poisoning:

1.Accidental ○ 2. Parasuicide ○

3. Homicide ○

Route of exposure:

1.Inhalation ○ 2. Cutaneous ○

3. Ingestion ○

Time lapsed between exposure & initial treatment (in hours)

CLINICAL FEATURES

Level of consciousness on arrival:

1.Alert. ○ 2. Drowsy. ○ 3. Irritable. ○
4. Unconscious ○

Effects of poisoning:

1.Nicotinic symptoms ○

Autonomic: Tachycardia ○ Hypertension ○

Metabolic acidosis ○

Skeletal muscle: Weakness ○ Fasciculations ○

Paralysis ○

2. Muscarinic symptoms ○

Smooth muscle constriction: Pupils ○

Bronchospasm ○

Glandular hyper-secretion: Lacrimal ○ Nasal ○

Sweating ○ Bronchial ○

Cardiac: Bradycardia ○ Shock ○

ADMISSIONS

Initial treatment:

1. PHC ○ 2. RMMCH ○

3. Other hospital ○

Admission area:

1. General ward ○ 2. RMMCH ICU ○ 3. Transfer to another ICU ○

Cholinesterase levels

1. Done ○ 2. Not done ○

Level:

OTHER INVESTIGATIONS (ON ARRIVAL):

Full blood count (FBC):

WCC Hb MCV

Platelet Count

Urea & Electrolyte (U&E):

Na K Cl HC03 Urea
Creat

Calcium Magnesium
Phosphate

Blood gas

pH pCO2 pO2 BE
HCO3 Lactate

Toxicology screen:

Done ○ Not Done ○
Findings

MANAGEMENT

Respiratory support

1.NPO2 ○ 2. Face mask O2 ○ 3. High Flow O2 ○ 4. NCPAP ○ 5. IPPV ○

Definitive

1.Atropine ○ 2. Glycopyrrolate ○ 3. Oximes ○ 4. Inotropes ○

Complications:

1.Arrhythmia ○ 2. Seizures ○ 3. Respiratory failure ○ 4. Coma ○

*Duration of stay (days):*_____

OUTCOME

1.Discharged 2. Transferred ○
3. Demised ○

Transferred out:

1.CHBAH MICU ○ 2. CMJAH ICU ○ 3. NMCH ICU ○_____
4.OTHER(SPECIFY)

3. ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Sibongile Dlamini

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190126

NAME: (Principal Investigator)	Dr Sibongile Dlamini
DEPARTMENT:	Paediatrics Rahima Moosa Mother and Child Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An analysis of children admitted with organophosphate and carbamate poisoning at Rahima Moosa Mother and Child Hospital
DATE CONSIDERED:	25/01/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Tim De Maayer
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/03/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authoriz to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore be due in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 08/04/2022

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES