

COMPARATIVE STUDY OF COMMONLY PRACTICED ATROPINIZATION REGIMENS IN ACUTE ORGANOPHOSPHORUS COMPOUND POISONING

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ABSTRACT

Aim of the study: Effect of atropinization with different methods. Outcomes in terms of duration of hospital stay and patients recovery. **Methodology:** An open-label randomized clinical trial was conducted in, Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka. 108 individuals with OPC poisoning. We compared two groups that used a titrated dosing protocol based on a structured monitoring sheet for atropine infusion with another group using an 'ad hoc' regime. The aim was to compare the efficacy and safety of conventional bolus doses with individualized incremental doses of atropine for atropinization followed by continuous atropine infusion for management of OPC poisoning. **Result:** Out of 108 patients, 54 patients received conventional bolus dose atropine (group A) and 54 patient received rapidly incremental doses of atropine followed by infusion (group B). 36 subjects analyzed in group A and 32 in group B for moderate to severe poisoning. The mortality in group A was 11.1%(4/36) and in group B was 6.3%(2/32). The mean duration of atropinization in group A was 5.8hrs (348) in minutes compared to time 26.9minutes for group B. **Conclusion:** Administration of atropine using a fixed algorithm is easy and effective in providing the atropine requirement in management of early phase of acute OPC poisoning. Rapid incremental dose atropinization followed by atropine infusion reduces mortality and morbidity from OPC poisoning and shortens the length of hospital stay and early recovery. Incremental atropine and infusion should become the treatment of choice for OPC poisoning.

KEYWORDS: Organophosphate compound; Atropine toxicity; Organophosphorus poisoning; Atropinization protocols.

INTRODUCTION

Organophosphorus poisoning is the most common poisoning in India and it is a common emergency health problem worldwide, particularly in developing countries and common means of attempting suicide because of its easy availability [1, 2]. It is one of the most common cause of severe toxicity and death with more than 3,00,000 death each year in developing countries [3]. Organophosphorus compounds most commonly used are dimethoate, dichlorovas, monocrotophos, chlorpyrifos, glyphosate, profenofos, malathion. Organophosphorus compounds inhibit both cholinesterase and pseudocholinesterase activities. The inhibition of acetylcholinesterase causes accumulation of acetylcholine at synapses and the resulting overstimulation of neurotransmission at the neuromuscular junction. It disturbs transmission at parasympathetic nerve end-

ings, sympathetic ganglia, neuromuscular endplates and CNS region [4, 5]. OP poisoning compound produce their effects by inhibiting the action acetylcholine esterase enzyme, which leads to an increase in acetylcholine, in preganglionic parasympathetic receptors (muscarinic action), sympathetic preganglionic synapses including adrenal medulla and neuromuscular junction (nicotinic action) [6].

Early diagnosis and appropriate treatment is often life-saving. Atropine is the mainstay of treatment of effects mediated by muscarine sensitive receptors. The primary outcome measure was mortality and secondary outcome measure were time to atropinization, total dose of atropine required, incidence of atropine toxicity, incidence of intermediate syndrome and duration of hospitalization [7].

MATERIALS AND METHODS

Study design: An open-label randomized Clinical trial.

Ethical approval: The study was approved by the institutional ethics committee and informed consent was taken from the patient/guardian.



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Study location: Study was conducted in Shri B. M. Patil Medical College Hospital & Research Centre, Vijayapura (BIJAPUR), Karnataka, India

Study duration: study was conducted from November 2015 to June 2017.

Sample size: 108 patients were included in the study.

Data of patients who are enrolled in the study collected from patient fulfilling inclusion and exclusion criteria attended both in ICU (Intensive care unit) and Emergency Ward.

Inclusion criteria: History of organophosphate poisoning (within 48hours of organophosphate poisoning and above age >18years) or signs of organophosphate poisoning (at least one of the following four signs bronchorrhea, miosis, fasciculation, bradycardia) and low serum cholinesterase level(less than 25%of normal) with moderate to severe poisoning.

Exclusion criteria: Admission after 48hours of poisoning, carbamates or other poisonings and patients with mild poisoning, patient with known systemic illness like malignancy, chronic lung disease, renal or hepatic disease and Pregnancy.

Methodology: An open label randomized clinical trial was conducted in SHRI B.M.PATIL MEDICAL College Hospital and Research Centre, Vijayapura (BIJAPUR), KARNATAKA, INDIA IN 108 hospitalized individuals. The patients were randomly divided into two groups (group A) SHRI B M PATIL MEDICAL COLLEGE AND Hospital and (group B) SOUTH ASIAN CLINICAL TOXICOLOGY RESEARCH COLLABORATION, we compared two groups that used a titrated dosing protocol based on a structured monitoring sheet for atropine infusion with another group using an ‘ad hoc’ regimen. The aim was to compare the efficacy and safety of conventional bolus doses with individualized incremental doses of atropine for atropinization, followed by continuous atropine infusion for management of OPC poisoning.

Out of 108 patients 54 patients received conventional bolus dose atropine (group A) and 54 patients received rapidly incremental dose of atropine followed by infusion (group B). 36 patients analyzed in group A and 32 patients in group B for moderate to severe poisoning.

Assessment of severity of poisoning: Muscarinic: Bradycardia, hypotension, bronchospasm, miosis, bronchorrhea, increased salivation, lacrimation, blurred vision,

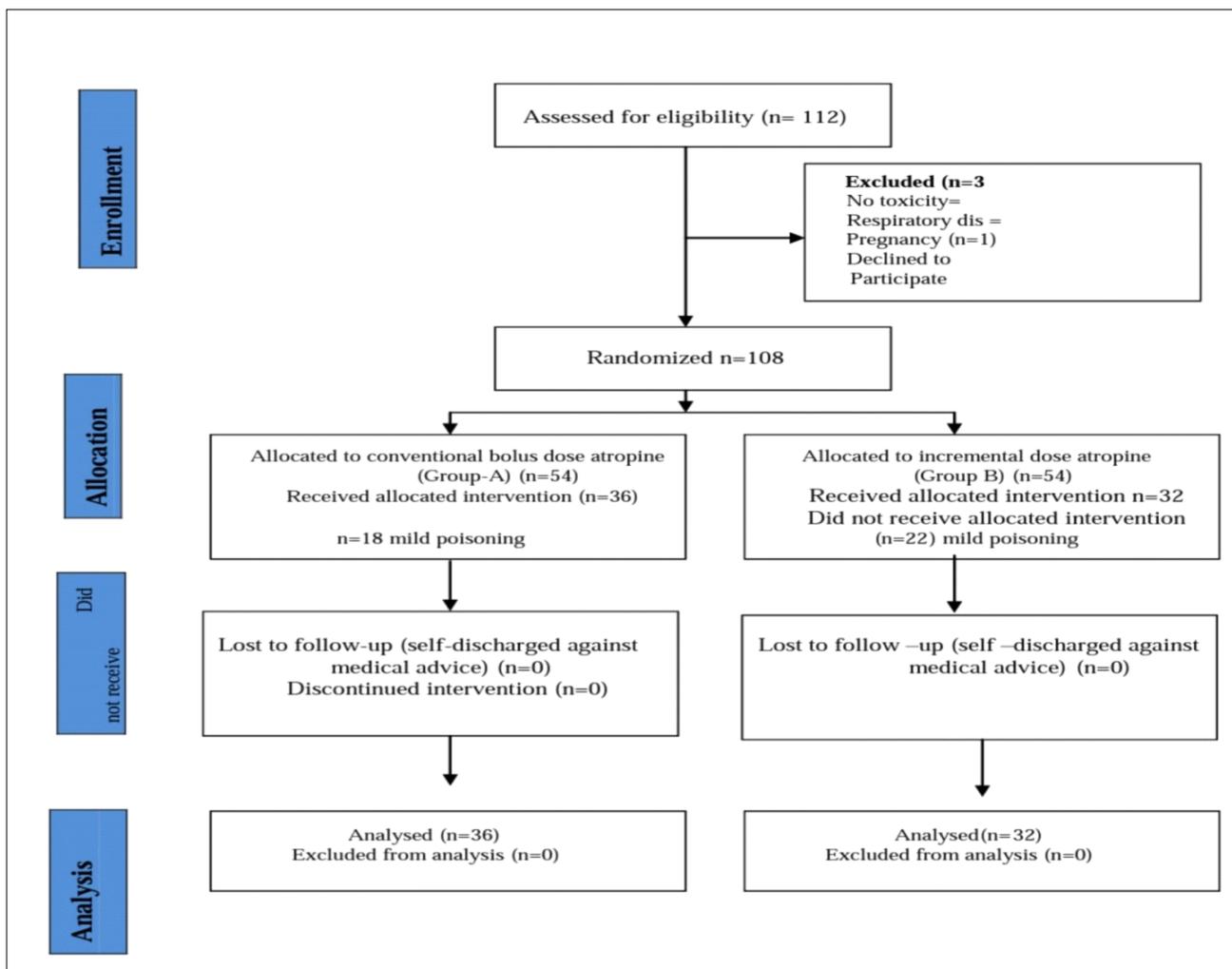


Figure 1. Consort Flow Diagram

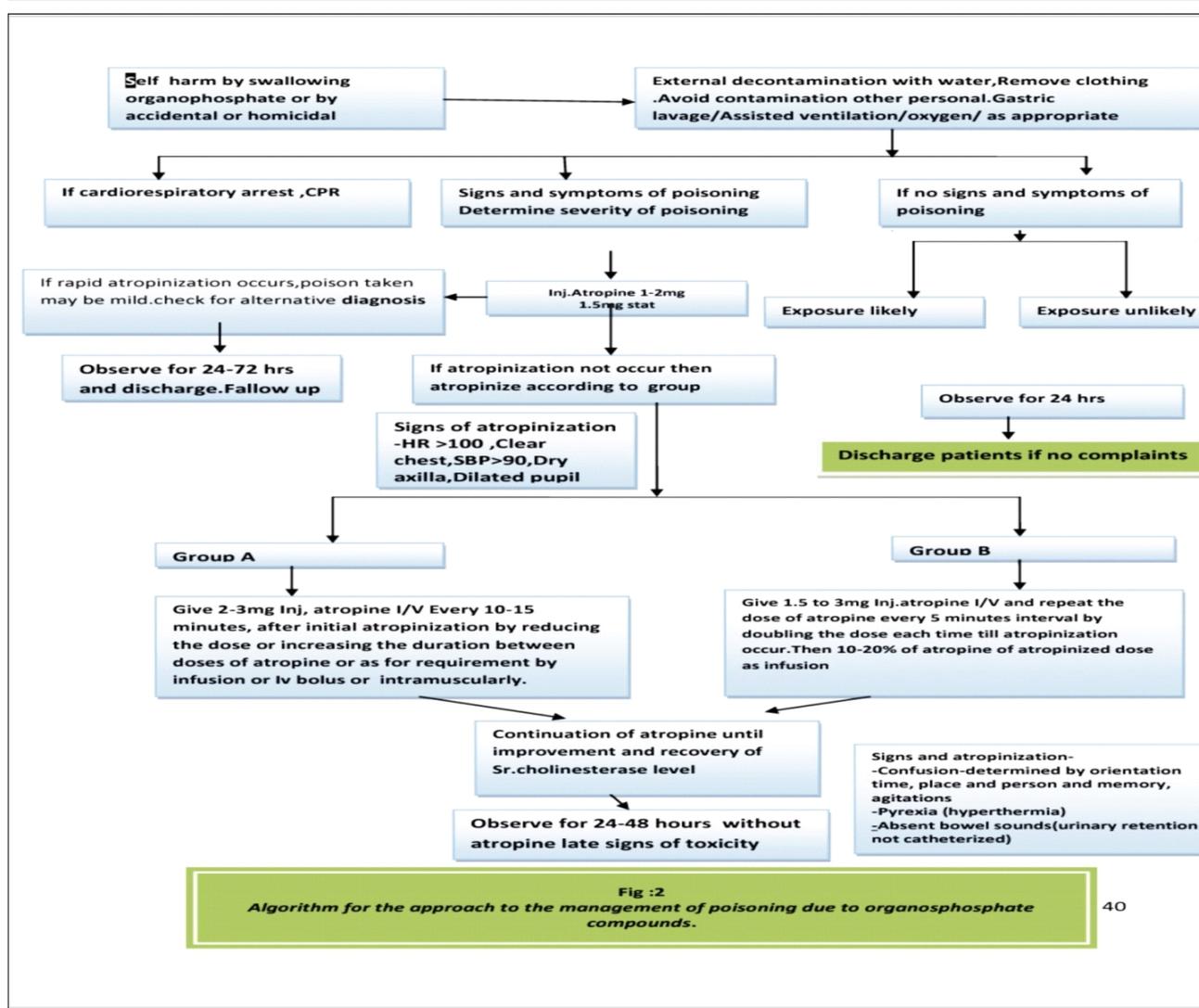


Figure 2. Treatment Procedure: [11, 12, 14]

nausea, vomiting, abdominal pain, diarrhoea, fecal and urinary incontinence, sweating [8, 9].

Nicotinic: Muscle fasciculation, cramping, weakness, diaphragmatic failure [10].

CNS: Anxiety, restlessness, confusion, ataxia, seizure, insomnia, dysarthria, tremor, coma [13].

GROUP A:

The number of patients received increasing doses of Injection Atropine 2-3mg every 10-15 minutes depending on severity of signs and symptoms as decision made by treating clinician. This was repeated every 10 to 15 min until signs of atropinization were clinically evident (clear chest on auscultation with resolution of bronchospasm, heart rate of >100 beats per minute, systolic blood pressure >90 mmHg, dry axillae and pupils >2mm in diameter) [14].

Injection Atropine 1cc= 0.6mg, that means 2-5cc of atropine had been repeated every 10-15 minutes until signs of atropinization[15]. This is followed by either intravenous infusion or bolus or intramuscular route

for maintenance every hourly according to clinically assessed and the subsequent dosing with atropine injections was individualized either by decreasing the dose or increasing the duration in between doses as per the preference provided as features of atropinization were still present[16, 17].

If one or all of these features were absent, the dose or frequency of atropine was increased as per the preference of the treating clinician. Atropinization was maintained for at least 24 hour until clinical recovery, i.e. till resolution of all features of cholinergic crisis occur.

Following the initial atropinization, patients had to be reassessed for the five features of atropinization every 15 minutes. When atropinization could not be achieved (bronchospasm or bradycardia, sweating and miosis) if still present, further bolus of atropine was administered. After atropinization, patients were observed at least every hour for 6 hours [19].

If atropine toxicity developed (confusion, pyrexia, absent bowel sounds; all three should be present), atropine was stopped and patients were closely monitored.

Table 1. Group B observation chart

Initials XXX	Study number Ipd RGN HR >100/mn	Date of admission XXX	Pupil size	Dry axilla	Systolic BP>100 mm of hg	Bowel sounds	CONFUSED A/D/N/I	FEVER>37.5 C	ATROPINE INFUSION Bolus? given	
		Clear lungs								BOLUS
Time										
22.3	52	Crepts+	PIn point	No	90/60	I	No	No		2.4
22.35	60	Crepts+	PIn point	No	90/60	I	No	No		4.8
22.4	82	+/-occ	PIn point	yes	100/60	N	No	No		4
22.5	100	WHEEZE	2mm	Yes	-	D	No	No		2
23	104	Clear	3mm	Yes	-	D	No	No	2	infuston
23.15	102	Clear	3- 4mm	Yes	-	D	No	No	2	infuston
23.3	102	Clear	3- 4mm	Yes	-	D	No	No	2	infuston
0.3	98	Clear	3- 4mm	Yes	100/70	D	No	No	2	infuston
1.3	85	Clear	3- 4mm	Yes	-	D	No	No	2	infuston
2.3	72	WHEEZE	3- 4mm	Yes	-	N/D	No	No		2
2.35	96	Clear	3- 4mm	yes	-	D	No	No	2.4	infuston
2.45	98	Clear	3- 4mm	Yes	-	D	No	No	2.4	infuston
4	102	Clear	3- 4mm	yes	-	D	No	No	2.4	infuston

An observation chart group B recording the initial atropinisation of an organophosphorus-poisoned patient

In case of a decline in heart rate to less than 100 b/m on day 1 and 60 b/m on day 2 onwards 2-3cc i.e. 1-2mg atropine intravenous boluses/ Intramuscular to be repeated every 15 minutes.

In case of persistent tachycardia HR > 120bpm atropine infusion can be lowered by 1 mg/h or assessed clinically.

GROUP B:

It consists of an initial bolus of 1.5 to 3 mg of atropine with doses doubling every 5 minutes until atropinization is achieved. Clearing of chest on auscultation was used as the primary endpoint of atropinization [18].

Following that an infusion is given with a rate that is estimated from the size of the initial dose required to

achieve atropinization. This is typically in the range of 1 to 2 mg/hour. Incremental dose was defined as 1.5–3 mg atropine by intravenous (IV) infusion, repeating the dose every 5 minutes interval, doubling the dose each time to the point of atropinization occurs, followed by 10–20% of atropine required for atropinization, every hour by IV infusion[19, 20, 21].

Example -2, 4, 8, 16,...etc every five minutes until atropinization, after initial atropinization, patients were maintained on an atropine infusion, using 10% of the atropine required to load the patient given per hour e.g. if atropine required for atropinization was 15 mg, 1.5 mg was Infused each hour by mixing the amount of atropine required for 24 h with 1,000 ml normal saline and giving it at a rate of 40 micro drops per minute as a continuous infusion [22-25].

Table 2. Demographic history; According to patient age, sex distribution, occupation, nature of poison, prior hospitalization, prior treatment and time between ingestion and hospitalization in OPC poisoning in group A and group B.

Variable	Group A- n (%)	Group B- n (%)	p value
Age (yrs)			
<20	10 -18.5	8-14.8	
20-29	24-44.4	27-50	
30-39	11-20.4	13-24.1	0.763
40-49	5-9.3	2-3.7	
>50	4-7.4	4-7.4	
Sex			
male	29-53.7	22-40.7	
female	25-46.3	32-59.3	0.177
Occupation			
business	4 -7.4	3-5.6	
farmer	17-31.5	15-27.8	
Housewife	13-24.1	22-40.7	
service	3-5.6	1-1.9	0.439
Student	14-25.9	9-16.7	
Unemployed	3-5.6	4-7.4	
Time between ingestion and hospitalization	Mean 4.1(in hours)	Mean 3.3(in hours)	
Op smell			
present	44-81.5	41-75.9	
Not present	10-18.5	13-24.1	0.481
Nature of poisoning			
Deliberate self harm	49-90.7	51-94	
other	9.3	6	
Prior gastric lavage			
not given	34-63	38-70.4	0.414
given	20-37	16-29.6	
Treatment prior to hospitalization	Atropine(out of 36)mod to severe	Out of 32	
no	24-66.7	26-81.3	
yes	12-33.3	6-18.8	0.174

Common treatment followed to both the groups: The poisoned patients were divided into three categories, mild, moderate and severe. Gastric lavage and adequate ventilation maintained. The stabilization was carried out in the emergency ward and patients were monitored using continuous ECG monitor, pulse oximetry and blood pressure, clinically assessed dehydration corrected with Intravenous fluids, oxygenation and catheterization before atropine was given. Pam (oximes) had been given to both groups. Treatment with pralidoxime was repeated as a bolus at the same dose and rate as the initial dose every 8 h for 48 h in all surviving patients as per standard practice [26].

Evidence of pralidoxime toxicity including tachycardia, muscular rigidity, neuromuscular blockade, hypertension, laryngospasm and mild hepatitis was recorded and managed by reducing the subsequent dose of pralidoxime and/or atropine as appropriate. Atropinization

followed according to group decided by treating team. Other supportive treatment had been made as for requirement like eye care, oral care, endotracheal tube care. Tracheostomy done in some patients who had longer period of ventilator supports. Routine investigations includes complete blood count, renal function test, liver function test, chest X RAY, random blood sugar, most importantly serum cholinesterase, which is one of the prognostic indicator for OPC poisoning [27].

Diagnosis of intermediate syndrome (IMS): Intermediate syndrome was defined as proximal muscle weakness of Grade 3 or less, 72 hours after poisoning with or without requirement of mechanical ventilation. All patients were monitored for early signs of IMS due to OPC poisoning. Signs of IMS were weakness of neck flexion, difficulty in lifting the head off the pillow, use of accessory muscles of respiration, nasal flaring, tachypnea, sweating, cranial nerve palsies and proximal limb mus-

Table 3. Atropine dose between study groups among 36 patients in group A and 32 patients in group B analyzed for moderate to severe poisoning

ATROPINE DOSES	GROUP A	GROUP B	P VALUE
	MEAN \pm SD	MEAN \pm SD	
0-2 hours	6.2 \pm 2.7	18.2 \pm 8.8	<0.001*
3-4 hours	6.0 \pm 3.5	3.6 \pm 2.8	0.003*
5-6 hours	5.9 \pm 3.2	5.2 \pm 3.1	0.343
7-8hours	6.0 \pm 3.7	6.5 \pm 3.2	0.552
9-24 hours	29.4 \pm 17.4	33.8 \pm 11.6	0.227
DAY 1 total	52.1 \pm 22.7	67.3 \pm 18.1	0.003*
DAY 2	23.6 \pm 18.5	31.5 \pm 11.8	0.047*
DAY 3	16.9 \pm 14.5	23.1 \pm 13.6	0.091
DAY 4	12.7 \pm 14.1	19.3 \pm 14.8	0.101
DAY 5	10.8 \pm 17.2	17.7 \pm 11.9	0.209
DAY 6	11.5 \pm 13.2	19.3 \pm 9.6	0.175
DAY 7	8.7 \pm 13.5	13.3 \pm 10.3	0.484
DAY 8	14.7 \pm 19.9	25.8 \pm 4.2	0.522

Table 4. Outcomes in terms of recovery, complication, atropine toxicity, mortality and IMS

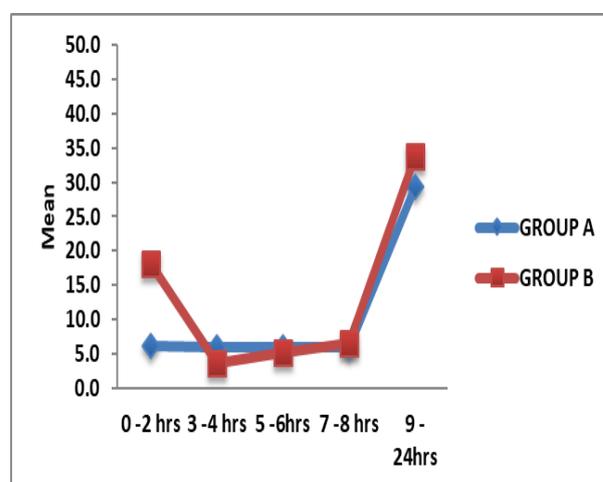
Outcome	Group A		Group B		Total N	P value
	N	%	N	%		
Complete recovery	31	50.8	30	49.2	61	0.301
Recovery with complications	5	62.5	3	37.5	8	0.564
Intermediate syndrome	9	69.2	4	30.8	13	0.048*
Atropine toxicity	9	64.3	5	35.7	14	0.027*
Mortality	5	71.4	2	28.6	7	0.031*

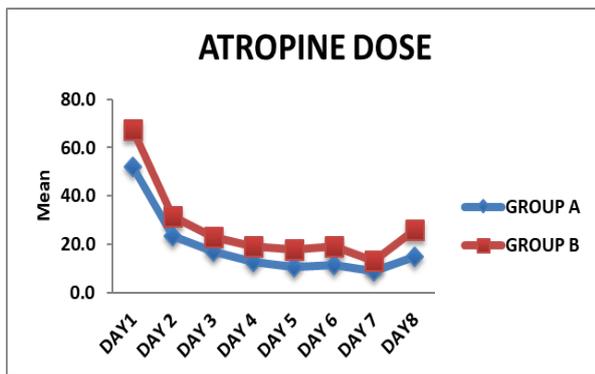
cle weakness with retained distal muscle strength. IMS was managed by supportive measures including intubation and ventilation if required. The patients were discharged after a minimum of 24 h of observation post cessation atropine if they had no residual features of OPC poisoning [28-30].

Markers of atropine toxicity: Confusion, pyrexia, absent bowel sounds or urinary retention were used mainly in the diagnosis of atropine toxicity [25-30].

Statistical analysis: Data were analyzed using SPSS software v.23.0. and Microsoft office. Chi-square/Freeman-Halton Fischer exact test was employed to determine the significance of differences between groups for categorical data. The differences of the means of analysis variables between two independent groups was tested by unpaired t test, p value was calculated and p value <0.05 were considered to be statistically significant.

RESULTS

**Graph 1. Atropine dose Day 1.**



Graph 2. Day 1 to Day 8.

Features on enrollment, there were 54 patients enrolled in group A and 54 in group B. 36 patients in group A and 32 patients in group B analyzed for moderate to severe poisoning.

Initial atropinization, In group A the mean atropine required for initial atropinization of a patient was 19.9mg. The mean time required for atropinization was 5.8 hours that is 348 minutes. Minimum time taken for atropinization was 2 hours and maximum 18 hours from 7.2mg to 43.2mg. Total mean atropine given initial 24hrs was 52.1 in 24 hours. In group B, the mean atropine required for initial atropinization was 18.2mg. The time required for atropinization was 28.1 minutes that is less than 1 hour. Mean atropine in day 1 was 67.3mg.

DISCUSSION

Atropine is the universally accepted specific treatment in the management of anticholinesterase poisoning [18-20]. In the study we found that rapid atropinization followed by atropine infusion greatly reduced mortality when compared to standard treatment with boluses of atropine 4 (11.1% in group A) versus 2 (6.3% in group B). When we compare group A, 4 of patients died compared to 2 in group B. In other study done previously had same outcomes where 45 cases of organophosphorus poisoning study showed that continuous infusion significantly reduced mortality compared to intermittent boluses (23.5% to 8.8%; $p < 0.05$) [21-22].

The similar study conducted on 131 sample shows that rapid incremental dose atropinization followed by atropine infusion reduces mortality and morbidity from OPC poisoning and shortens the length of hospital stay and recovery advantage over conventional incremental bolus doses alone (24.7% versus 8%; $p < 0.05$) [23]. The study conducted on 56 patient shows frequency of atropine toxicity in the rapid incremental regimen followed by infusion (1.8%) was considerably lower than conventional regimen [24].

The relatively few formal trials in OPC poisoning that have been done to make it clear that early antagonism of OPC toxicity is associated with better outcome [25]. Full and early atropinization is ideal as delayed atropinization can result in death from central respiratory de-

pression, bronchospasm, bronchorrhea, severe bradycardia and hypotension [26]. The time interval between exposure to OPC poisoning and onset of symptoms of poisoning varies with route and degree of exposure. Following massive ingestions, the symptoms appear within several minutes [27]. With smaller amounts, in most instances, symptoms appear within 30 minutes of exposure and almost always in less than 12 hours [28].

In our series, the earliest presentation of an individual with features of toxicity was within 30 minutes of ingestion of OPC, although 25% took more than 4 hours to reach the hospital. Delay in discovery and transport to the hospital as well as differences in treatment seeking behaviour can cause differences in presentation and increased mortality. Local effects on eyes and respiratory tract may appear within minutes. After ingestion of OPC, the initial symptom may be gastrointestinal or may be related to any other organs affected [26]. Regimen B was found to be associated with a lower risk of developing IMS ($P < 0.05$) [28-30]. Ventilation support was needed for 18 patients out of 68. Of these 12, survived. In other studies, the survival rate in OPC poisoning requiring mechanical ventilation varied between 13% and 50% in a variety of settings. Ventilator support was required in significantly fewer patients treated with regimen B [30-34].

The occurrence of atropine toxicity also compared between the treatment groups [35-38]. Patient treated with conventional bolus dose were found to be more at risk of developing atropine toxicity (25% versus 12.5%, $p < 0.05$). Previous studies have found similar rates with bolus regimen (26%) [35-40].

CONCLUSION

Use of atropine for organophosphorus poisoning given by individualized incremental bolus doses followed by continuous infusion has several advantages over conventional incremental bolus doses alone. Early atropinization reduces mortality and atropine toxicity which leads to better hospital outcome and recovery. Accurate and frequent monitoring is required in conventional incremental bolus dosing regimen for atropinization and toxicity.

Limitation: The study was done on small number of patients and involved moderate to severe poisoning. Many patients enrolled into the study were referred from a peripheral hospital and treatment received there might have had some influence on the requirement of atropine.

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