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Comparative Study of Current Dosing Practice of Atropine in Organophosphorus Poisoning at BLDE University Shri B M Patil Medical College and Hospital With Protocol Administration Practised at South Asian Clinical Toxicology Research Collaboration.

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ABSTRACT

Background: 1.Effect of atropinization with different methods.2.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 Reasearchcentre, Vijyapura, Karnataka in 108 individuals with OPC poisoning .We compared two groups that used a titrated dosing protocol based on a structured monitoring sheet for atropineinfusion with another group using an 'ad hoc' regime. The aim was to compare the efficacy andsafety of conventional bolus doses with individualized incremental doses of atropine for atropinization followed by continuous atropine infusion for management of OPC poisoning. **Results**: 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 analysed 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: Atropine, Organophosphorus Poisoning, Toxicology.

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. 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. Organophosphorus compounds most commonly used are dimethoate, dichlorovas, monocrotophos, chlorpyrifos, glyphosate, profenofos, malathion.

Organophosphorus compounds inhibit both cholinesterase and pseudocholinesteraseactivities. The inhibition of acetylcholinesterase causes accumulation of acetylcholine at synapses and the resulting overstimulation of neurotransmission at the neuromuscular junction, disturbs transmission at parasympathetic nerve endings, sympathetic ganglia, neuromuscular endplates and CNS region. 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).

Early diagnosis and appropriate treatment is often lifesaving. 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.

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MATERIALS AND METHODS

Source of Data:

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. An open-label randomized Clinical trial was conducted in SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE, VIJAYPURA (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, that used a titrated dosing protocol of atropine.

Inclusion criteria

1. History of organophosphate poisoning(within 48hours of organophosphate poisoning and above age >18years) or signs of organophosphate poisoning (atleast one of the following four signs – bronchorrhea, miosis, fasciculation, bradycardia)and
2. Low serum cholinesterase level(less than 25%of normal) with moderate to severe poisoning.

Exclusion criteria

1. Admission after 48hours of poisoning.
2. Carbamate or other poisonings and patients with mild poisoning.
3. Patient with known systemic illness like malignancy, chronic lung disease, renal or hepatic disease.
4. Pregnancy

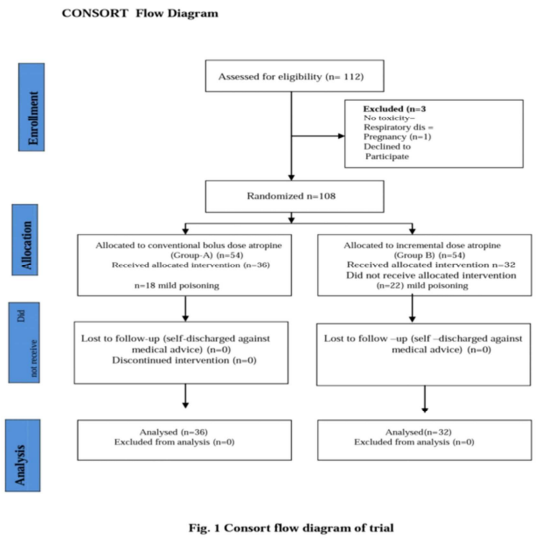

Fig. 1 Consort flow diagram of trial

Figure 1:

Assessment of severity of poisoning: muscarinic

Bradycardia, hypotension, bronchospasm, miosis, bronchorrhea, increased salivation, lacrimation, blurredvision, nausea, vomiting, abdominal pain, diarrhoea, fecal and urinary incontinence, sweating.

Nicotinic: Muscle fasciculation, cramping, weakness, diaphragmatic failure.

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

Treatment Procedures

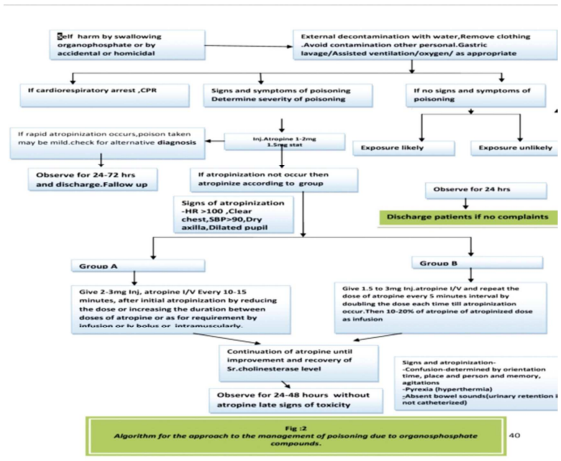

Figure 2:

GROUP A

The number of patients received increasing doses of Inj. 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 bronchorrhea, heart rate of >100 beats per minute, systolic blood pressure >90 mmHg, dry axillae and pupils >2mm in diameter).

Inj. atropine 1cc= 0.6mg, that means 2-5cc of atropine had been repeated every 10-15 minutes until signs of atropinization.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.

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 everyhour for 6 hours.

If atropine toxicity developed (confusion, pyrexia, absent bowel sounds; all three should be present), atropine was stopped and patients were closely monitored.In case of a decline in heart rate to less than 100 bpm on day 1 and 60 bpm 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 atropinisation is achieved. Clearing of chest on auscultation was used as the primary endpoint of atropinization.

Following that an infusion is given with a rate that is estimated from the size of the initial dose required to achieve atropinisation.This is typically in the range of 1 to 2 mg/hour. Incremental dose wasdefined as 1.5–3 mg atropine by intravenous (IV) infusion, repeating the dose every 5minutes 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.

Eg -2,4,8,16,…etc every five minutes until atropinization, after initialatropinization, 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.

Table 1:

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 poin	No	90/60	I	No	No		4.8
22.4	82	+/-occ	Pin poin	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

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.

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.

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 muscle 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.

Markers of atropine toxicity

Confusion, pyrexia, absent bowel sounds or urinary retention were usedmainly in the diagnosis of atropine toxicity.

RESULTS

Table 2:

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

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 analysed for moderate to severe poisoning.

Demographic history

According to patients 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.

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

ATROPINE DOSE	GROUP A		GROUP B		p value
	Mean	SD	Mean	SD	
0 -2 hrs	6.2	2.7	18.2	8.8	<0.001*
3 -4 hrs	6.0	3.5	3.6	2.8	0.003*
5 -6hrs	5.9	3.2	5.2	3.1	0.343
7 -8 hrs	6.0	3.7	6.5	3.2	0.552
9 - 24hrs	29.4	17.4	33.8	11.6	0.227
DAY1 total	52.1	22.7	67.3	18.1	0.003*
DAY 2	23.6	18.5	31.5	11.8	0.047*
DAY 3	16.9	14.5	23.1	13.6	0.091
DAY 4	12.7	14.1	19.3	14.8	0.101
DAY 5	10.8	17.2	17.7	11.9	0.209
DAY 6	11.5	13.2	19.3	9.6	0.175
DAY 7	8.7	13.5	13.3	10.3	0.484
DAY8	14.7	19.9	25.8	4.2	0.522

* 5% level of significance (p<0.05)

Initial atropinization ,In group A the mean atropine required for initial atropinization of a patient was 19.9mg.The mean time requires for atropinizationwas 5.8hours that is 348minutes.Minimum time taken for atropinization was 2hours and maximum 18hours from 7.2mg to 43.2mg.Total mean atropine given initial 24hrs was 52.1 in 24hours.In group B, the mean atropine required for initial atropinization was18.2mg.

The time required for atropinization was 28.1minutes that is less than 1hour.Mean atropine in day 1was 67.3mg.

Table 4: Outcomesinterms of recovery, complication, atropinetoxicity, mortality and IMS.

Outcome	Group A		Group B		Total	P value
	N	%	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*

Note: * significant at 5% level of significance (p<0.05)

DISCUSSION

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).

Duration of hospital stay more or less same in both groups.Time taken for atropinization in group A is mean 348minutes (5-6hours) and group B (28.3minutes). IMS developed in 14 patients among whom the offending OPC agent was identified in 8 of these 4 ingested malathion,2 ingested dichlorovos and 2 ingested dimethoate .

Regimen B was found to be associated with a lower risk of developing IMS (P<0.05).Ventilation support was needed for 18 patients out of 68. Of these 12, survived. In other studies,the survival rate on OPC poisoning requiring mechanical ventilation varied between 13%and 50%in a variety of setting. Ventilator support was required in significantly fewer patients treated with regimen B.

The occurrence of atropine toxicity also compared between the treatment groups. Patient treated with conventional bolus dose were found to be more at risk of developing atropine toxicity (25%versus 12.5%,p<0.05%).

CONCLUSION

1. 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.
2. Earlyatropinization reduces mortality and atropine toxicity which leads to better hospital outcome and recovery.
3. Accurate and frequent monitoring is required in conventional incremental bolus dosing regimen for atropinizationand toxicity.

Limitation

1. The study was done on small number of patients and involved moderate to severe poisoning.
2. 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.

REFERENCES

1. Jeyaratnam J: Acute pesticide poisoning: a major global health problem. WldHlth Statist Q 1990, 43:139-144.
2. Eddleston M: Patterns and problems of deliberate self-poisoning in the developing world. Q J Med 2000, 93:715-731.
3. Eddleston M, Phillips MR: Self poisoning with pesticides. BMJ 2004, 328:42-44.
4. Buckley NA, Karalliedde L, Dawson A, et al. Where is the evidence for the management of pesticide poisoning – is clinical toxicology fiddling while thedeveloping world burns? J ToxicolClinToxicol 2004,42: 113-116.
5. EddlestonM,SheriffMH,HawtonK.Deliberateself harm in Sri Lanka :an overlooked tragedy in the developing world .BMJ.1998 Jul11;317(7151):133-5.
6. Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. QJM. 2000 Nov; 93(11):715-31.

7. Srinivas RaoCh, Venkateswarlu V, Surender T, et al. Pesticide poisoning in South India: opportunities for prevention and improved medical management: Tropical Medicine and International Health,June 2005:581-85.
8. Basic and Clinical Toxicology of Organophosphorus Compounds Editors: Balali-Mood, Mahdi, Abdollahi, Mohammad (Eds.)2014 ,257,p31,isbn;978-1-4471-5624-6.
9. Kalkan S, Erdogan A, Aygoren O, Capar S, Tuncok Y. Pesticide poisonings reported to the drug and poison information center in Izmir, Turkey. Vet Hum Toxicol 2003;45:50-2.
10. Siva PV, Padma VSA, Sarma DVHS, Reddy SM. Activity of Serum Cholinesterase in Organo - Phosphorus poisoning cases: A prospective study.JPharmaceutical Biomed Sci 2012;20(03):1-3
11. International Programme on Chemical Safety Antidotes for Poisoning by Organophosphorus Pesticides. Monograph on Atropine 2002[http://www.intox.org/databank/documents/antidote/antidote/atropine.htm].
12. Heath AJW, Meredith T: Atropine in the management of anticholinesterase poisoning. In Clinical and experimental toxicology of organophosphates andcarbamates Edited by: Ballantyne B, Marrs T. Oxford: Butterworth Heinemann; 1992:543-554.
13. Wadia RS, Sadagopan C, Amin RB, et al. Neurological manifestations of organophosphorous insecticide poisoning. J NeurolNeurosurg Psychiatry. 1974 Jul;37(7):841-7.
14. Eddleston M, Dawson A, Karalliedde et al. Early management after selfpoisoning with an organophosphorus or carbamate pesticide - a treatmentprotocol for junior doctors.Crit Care. 2004 Dec;8(6):R391-7. Epub 2004 Sep 22.
15. Bird SB, Gaspari RJ, Dickson EW: Early death due to severe organophosphate poisoning is a centrally mediated process. AcadEmerg Med 2003, 10:295-298.
16. Dickson EW, Bird SB, Gaspari RJ, et al. Diazepam inhibits organophosphateinduced central respiratory depression. AcadEmerg Med 2003, 10:1303-1306.deAlwis LBL, Salgado MSL: Agrochemical poisoning in Sri Lanka Forensic SciInt 1988, 36:81-89.
17. Eddleston M, Buckley NA, Checketts H, et al: Speed of initial atropinisation in significant organophosphorus pesticide poisoning--a systematic comparison of recommended regimens. J ToxicolClinToxicol. 2004; 42(6):865-75.
18. J Sunder Ram, SS Kumar, A Jayarajan, et al. Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning. J Assoc Physicians India 1991, 39: 190-193.
19. KF Schulz, I Chalmers, RJ Hayes, et al: Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995, 273: 408-412.
20. R Kunz, AD Oxman: The unpredictability paradox: review of empirical comparisons of randomised and nonrandomised clinical trials. BMJ 1998, 317: 1185-1190.
21. Open-Label Randomized Clinical Trial of Atropine Bolus Injection Versus Incremental Boluses Plus Infusion for Organophosphate Poisoning in Bangladesh Mohammed JoynalAbedin& Abdullah Abu Sayeed&Ariful Basher & Richard J Maude &GofranulHoque& M. A. Faiz Published online: 17 February 2012# American College of Medical Toxicology .

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