DISSERTATION ON

MULTIPLE-DOSE ACTIVATED CHARCOAL FOR TREATMENT OF YELLOW OLEANDER POISONING: A SINGLE - BLIND, RANDOMISED, PLACEBO -CONTROLLED TRIAL

Submitted in partial fulfilment of

Requirements for

M.D. DEGREE BRANCH I GENERAL MEDICINE

Of

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003.

FEBRUARY 2006

CERTIFICATE

This is to certify that this dissertation entitled "**MULTIPLE-DOSE ACTIVATED CHARCOAL FOR TREATMENT OF YELLOW OLEANDER POISONING: A SINGLE - BLIND, RANDOMISED, PLACEBO -CONTROLLED TRIAL**" submitted by **Dr. ABHILASH. S. P,** appearing for part II MD Branch I, General Medicine Degree Examination in February - March 2006 is a bonafide record of work done by him under my direct audience and supervision in partial fulfilment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, I forward this to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled "MULTIPLE-DOSE ACTIVATED CHARCOAL FOR TREATMENT OF YELLOW OLEANDER POISONING: A SINGLE - BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL" is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2004-2005 under the guidance and supervision of Prof. V. Sundaravadivelu, M.D.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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ACKNOWLEDGEMENT

I would like to thank our beloved Dean, Prof**.** KALAVATHI PONNIRAIVAN**,** M.D. for having given me permission to conduct this study and allowing me to utilise the resources of Madras Medical College & Government General Hospital, Chennai.

I would like to express my sincere gratitude to my beloved Professor and Director, Institute of Internal Medicine Prof. D.D. JAYAKUMAR, M.D. for his guidance and encouragement.

With extreme gratitude I express my indebtness to Prof. V. SUNDARAVADIVELU, M.D. for his motivation, advice and valuable criticism which enabled me to complete this work.

I am extremely grateful to Prof C. RAJENDRAN, M.D. for granting me permission to conduct this study at IMCU and poison centre and for his constant encouragement.

My sincere thanks to Assistant professors of Medicine Dr. R. Penchalayaih, M.D, Dr. K.V.S.Latha, M.D. and Dr. Sathyanarayanan, M.D. for their guidance and support.

I thank Dr. Mary Ramola M.D., Assistant professor social and preventive medicine, for her immense help in statistical analysis.

I am thankful to Dr. Arumugam M.D. post graduate student in D.M. Cardiology for his valuable support and suggestions.

I would always remember with extreme sense of thankfulness, the co-operation and criticism shown by my post graduate colleagues.

And finally, I am immensely grateful to the generosity shown by the patients who participated in this study, without them the study would not have been possible.

CONTENTS

INTRODUCTION

Yellow oleander poisoning is the most common plant poisoning in South India. It being a cardiac glycoside has significant cardiac toxicity and a mortality rate of about 10%[1]. In Madras Medical College, Chennai, Poison Centre alone, there were 210 persons admitted with oleander poisoning during the period September 1, 2001 to May 31, 2004 with a mortality rate of 11.43%[2].

Specialized treatment with antidigoxin fab fragments and cardiac pacing is expensive and not widely available. Multiple dose activated charcoal binds cardiac glycosides in the gut lumen and promotes their elimination. Aim of the study was to assess the efficacy of multiple dose activated charcoal in the treatment of patients with yellow oleander poisoning.

During the period June 1, 2004 to May 31, 2005 there were 63 cases of yellow oleander poisoning at the IMCU / Poison Centre of Madras Medical College, Chennai and the study included 47 patients who met the inclusion criteria.

OBJECTIVES OF THE STUDY

Aim of the study was to assess between the two arms of the trial whether:

a) Any significant reduction in mortality.

b) Any reduction in occurrence of major or life threatening cardiac arrhythmias.

c) Any reduction in the doses of other drugs-atropine- needed.

d) Any significant reduction in the number of days of stay in the hospital.

REVIEW OF LITERATURE

In nature a wide variety of cardiotonic steroids is found in plants, the insects that feed on them and in the parotid glands and skin of some toads. All these natural drugs contain a steroid nucleus with a lactone ring, five membered in the case of cardenolides, and six membered in bufadienolides.

The cardiac glycosides have a carbohydrate or sugar moiety attached through an oxygen bridge to carbon 3 of the ‘A’ ring of the steroid.

Mechanism of action of cardiac glycosides

The myocardial effects of these compounds are attributable to inhibition of transmembrane Na^+ / K^+ ATPase pump[3].

Cardiac glycosides bind selectively to extra cellular face of the membrane associated Na^+ K^+ ATPase of myocardial fibres and inhibits

this enzyme. This indirectly results in intracellular Ca^{2+} accumulation.

During depolarization Ca^{2+} ions enter the cell driven by the steep Ca^{2+} gradient through voltage sensitive Ca^{2+} channels. This triggers release of Ca^{2+} stored in sarcoplasmic reticulum and a fraction is extruded by 3 Na^{+} / 1 Ca^{2+} exchange. During the phase 3 of action potential membrane Na^{+} / K^{+} ATPase move 3 intracellular Na^{+} ions for 2 extracellular K^{+} ions.

The increase in cytostolic Na^{+} over normal due to inhibition of Na^{+} K^{+} ATPase by cardiac glycosides reduces transmembrane gradient of Na^{+}, which drives extrusion of Ca^{2+}. The excess Ca^{2+} remaining in cytosol are taken up by sarcoplasmic reticulum which progressively get loaded with more and more Ca^{2+} resulting in increase force of contraction of heart and conduction abnormalities. In addition, depletion of intracellular K^{+} aggravates the conduction disturbances.

Oleander plant & poisoning

The ‘Apocyanaceae’ are sources of African arrow poisons and also contain many of the most beautiful but deadly tropical flowering shrubs such as ‘Nerium Oleander’, pink or white oleander and ‘Thevetia peruviana’, yellow oleander[4].

Ingestion of oleander seeds or leaves is a common cause of accidental poisoning worldwide, particularly among children[5]. The oleander seeds have been used for suicide, homicide, abortion and as herbal remedies in India, Thailand, Brazil and elsewhere[6]. Cases of oleander poisoning have been reported from places as diverse as Hawaii, Southern Africa, Australia, Europe the Far East and the United States.

Deliberate self poisoning with seeds of yellow oleander is extremely common in South India and Sri Lanka. Yellow oleander glycosides proved effective in patients with heart failure and atrial fibrillation in studies carried out in the 1930s[7] and more recently in

India. However, digitoxin or oubain have been preferred because of less frequent gastrointestinal side effects.

White or sweet scented oleander

Nerium Odorum or sweet-scented oleander belongs to Apocyanaceae, and is grown in India for its beautiful white or pink flowers' which are given as offerings in temples. It has lanceolate leaves and has a two follicled fruit which contains numerous seeds.

All plants of the plant are poisonous. S R Naidu and his co-workers have isolated from the plant an active principle, nerin ($C_{35}H_{50}O_{10}$), which is a pure, white, crystalline glycoside with digitalis like action. It is sparingly soluble in water, ether, petroleum ether and benzene, but dissolves readily in alcohol, acetone and chloroform, and melts at 123 degree Celsius.

The plant, especially the leaf, bark and flowers are used to treat several diseases like skin diseases, infected wounds, snake bite, dysmenorrhoea, epilepsy etc.

Symptoms

Symptoms of oleander poisoning include gastrointestinal irritation and digitalis like action on the heart. There is also difficulty in swallowing and articulation, abdominal pain, vomiting, profuse frothy salivation and diarrhoea.

The pulse is slow and later becomes rapid and weak. Cardiac arrhythmias may develop. Respiration is quick, followed by dilated pupils, muscular twitchings, tetanic spasms, drowsiness, unconsciousness, coma and death. Lockjaw frequently occurs.

Fatal dose

It is not certain what quantity of white oleander will prove fatal. About 16.6 gram of the root may be considered an average fatal dose for an adult, though there have been instances where a little more than 4 gram of the bark have produced lethal poisonous symptoms.

Yellow Oleander

'Thevetia Peruviana" or yellow oleander is a plant belonging to Apocyanaceae, and is widely cultivated as an ornamental shrub in gardens in the plains in India. It has linear lanceolate leaves[8,9], large, yellow bell-shaped flowers and a green globular fruit containing a single nut, light brown in colour and triangular in shape with two cells, each enclosing a pale yellow seed.

The toxins

The yellow oleander contains atleast eight different cardiac glycosides, including thevetin-A, thevetin-B (cerberoside), thevetoxin, nerifolin, peruvoside and ruvoside.[6,9] All parts of the plant are dangerous, especially the seeds.

Thevetin $C_{27}H_{84}O_{12}$ is sparingly soluble in water, but dissolves readily in ether and chloroform, and melts at 178°C.[10]

Its paralytic action is not so well marked as that of 'nerin', the active principle of Nerium Odorum, the white oleander.

Ghatak[11] isolated from the kernels of the seeds of yellow oleander, thevetin and thevetoxin. The first glycoside, thevetin was obtained in the form of snow white, slender needles melting at 192°C by recrystalization from dilute alcohol.

The second glycoside, thevetoxin; when recrystallised twice from hot water was obtained in slender, shining, silky needles melting at 178°C. Both the glycosides were thought to be highly poisonous, but Bhatia and Lall[12] have demonstrated from experiments that thevetoxin is less toxic than thevetin. Prof. S. Rangaswami has isolated peruvoside, said to be one of the world's best cardiac drug from yellow oleander.

Fatal dose

It is not certain what constitutes a fatal dose of yellow oleander. One to two seeds may be fatal to a child where as eight to ten seeds are considered to be fatal in an adult[10,13].

Clinical features

Symptoms of poisoning include a burning pain in the mouth and dryness of the throat, tingling and numbness of the tongue, vomiting and often diarrhoea, headache, dizziness, dilated pupils and fainting. Ataxia, seizures and hypotension may also occur. Varying degrees of heart block and collapse sets in and death can occur.

Cardiac arrhythmias in oleander poisoning

Most cases of cardiac glycoside poisoning reported in the literature have been in patients overdosed during digitalis therapy for cardiovascular disease[14]. Eddleston et al[15] reported that they found clear differences in the incidence of particular arrhythmias between oleander and digitalis poisoning.

Ventricular ectopics and tachycardias are common in digoxin poisoned patients, but are rare in oleander poisoned patients, who are normally young and previously healthy. Among 89 seriously ill patients 53% had AV node conduction block, white 62% had sinus

node block; 30% had conduction block affecting both nodes. Only 1% had ventricular tachycardias and 8% had ventricular ectopics. These differences may be explained in part by the Serum K^+ levels before glycoside ingestion.

Most patients with severe digitalis poisoning have pre-existing hypokalemia attributable to the many other drugs that they are taking. Few of the patients who ingested yellow oleander were on any medication, and would have been normokalemic before the poisoning.

Severe oleander poisoning was associated with elevated serum potassium levels[16]. A similar relationship has been found in patients taking large suicidal overdoses of digoxin[17,18], and those ingesting toad skin poisons[19]. This is explained by inhibition of the Na^+ / K^+ ATPase pump by the cardiotoxic steroids.

Treatment of oleander poisoning

Routine treatment in our hospitals is gastric lavage and one oral dose of activated charcoal on admission, followed by intravenous

atropine, isoprenaline or both for bradyarrhythmias. Patients who do not respond to this treatment are given temporary cardiac pacing, often in a special unit, to which they must be transferred.

Eddleston and colleagues[20] have shown that antidigoxin antibody fab fragments can reduce life threatening cardiac arrhythmias and the need for cardiac pacing in oleander poisoning. However, their study was too small to determine whether treatment with the antibody had an effect on death rates. Furthermore, the use of the antibody is limited by its high cost and because it is rarely available in the rural and secondary care hospitals in which the patients with yellow oleander poisoning seek treatment.

At present patients with oleander poisoning who come to rural health centres are transferred to nearest secondary hospital for routine treatment and cardiac monitoring. Those showing evidence of cardiac conduction block are then transferred as quickly as possible to CCU for temporary cardiac pacing.

The cost of transfers together with temporary pacemakers and CCU beds is very high. Moreover a significant number of patients die before they reach CCU.

This indicates that a form of treatment appropriate for rural hospitals is urgently required. H.A. de Silva and colleagues[21] had shown that multiple dose activated charcoal is effective in reducing deaths and life threatening cardiac arrhythmias after yellow oleander poisoning. It could also reduce the cost of treatment.

Multiple dose activated charcoal

Activated charcoal is inexpensive and widely available. Charcoal adsorbs ingested poison within the gut lumen, allowing the charcoal-toxin complex to be evacuated with stool. The complex can also be removed from the stomach by induced emesis or lavage.

In vitro, charcoal adsorbs ≥ 90% of most substances when given in an amount equal to 10 times the weight of the substance[22]. Repetitive oral dosing with charcoal can enhance the elimination of

previously absorbed substances by binding them within the gut as they are excreted in the bile, secreted by gastrointestinal cells or passively diffuse in to the gut lumen (reverse absorption or enterocapillary exsorption).

After absorption into the systemic circulation, cardiac glycosides such as digoxin are secreted into the gut lumen by the action of P-Glycoprotein. In the gut, activated charcoal binds the secreted glycoside and encourages further secretion, there by causing a rise in glycoside excretion.

In pigs, repeated doses of activated charcoal reduced the half life of digoxin given intravenously from 65 hours to 17 hours and increased clearance from 2.3 ml/minute/kg to 7.1 ml/minute/kg[23].

In ten healthy volunteers who received intravenous digoxin, repeated doses of activated charcoal increased total body clearance from 12 L/hour to 18 L/hour and reduced the half life from 37 hours to 22 hours[24]. In addition Dasgupta et al demonstrated the efficacy of

activated charcoal in removing oleander leaf extract and oldeandrin from human serum by measuring apparent digoxin concentration.[25]

Side effects of activated charcoal, though not frequent, include mechanical obstruction of the airway, aspiration, vomiting and bowel obstruction and infarction caused by inspissated charcoal.

MATERIALS AND METHODS

Patients

Patients admitted during the period, June 1, 2004 to May 31, 2005 to the poison centre of Madras Medical College, Chennai, were included for the trial. Patients aged 12 – 70 years who were admitted within 24 hours of ingestion of yellow oleander seeds were eligible for inclusion.

Patients who had taken another drug such as alcohol, organophosphates, paracetamol or sedatives, had other debilitating diseases like diabetes mellitus, hepatic or renal disease, heart failure or malignant disease, had abdominal surgery within the past 1 year were excluded from the trial.

Patients with known hypersensitivity to activated charcoal, those with severe infections and pregnant and lactating women also excluded. Patients who received corticosteroids as part of treatment,

as suggested by cardiologist, were also excluded from the study, to avoid confounding.

Patients were informed about the nature, objectives, importance, expected benefits and possible adverse effects of the treatment. If the patient did not give the consent, permission from a parent, spouse or guardian was sought. Patients were told they were free to withdraw from the trial at any time if they wished to do so, without any prejudice to subsequent management.

Procedures

On admission, all patients were assessed and received standard treatment of yellow oleander poisoning i.e., gastric lavage, one 50g dose of activated charcoal, and atropine as needed. Cardiopulmonary resuscitation was given when required. Concentrations of serum potassium, sodium, and creatinine and blood urea were measured at base line, did electrocardiographs serially and monitored the cardiac rhythm. Patients were assessed and treated throughout the trial in accordance with a standardised management protocol (given separate).

6 hours after admission patients were randomly allocated either multiple doses of activated charcoal (50g) or placebo (sterile water) every 6 hours. The investigator was not involved in the patient allocation into the two arms. Also he was unaware of the patient's treatment allocation during the trial.

Patients were asked to drink the activated charcoal or sterile water and used a nasogastric tube for those who were unable to do so. The poison centre staffs, who supervised administration of activated charcoal or sterile water, did not participate in clinical assessment or management of patients.

Activated charcoal was given in a dose of 50g dissolved in water to 400ml every 6 hours for 3 days. An equivalent amount of sterile water was given to those on placebo. Patients who had nausea or vomiting after the trial began were given 10mg of intravenous metoclopramide as required. Patients were monitored for abnormalities in cardiac rhythms and electrocardiograms were done if arrhythmias were detected. Patients were monitored until discharge from hospital or death.

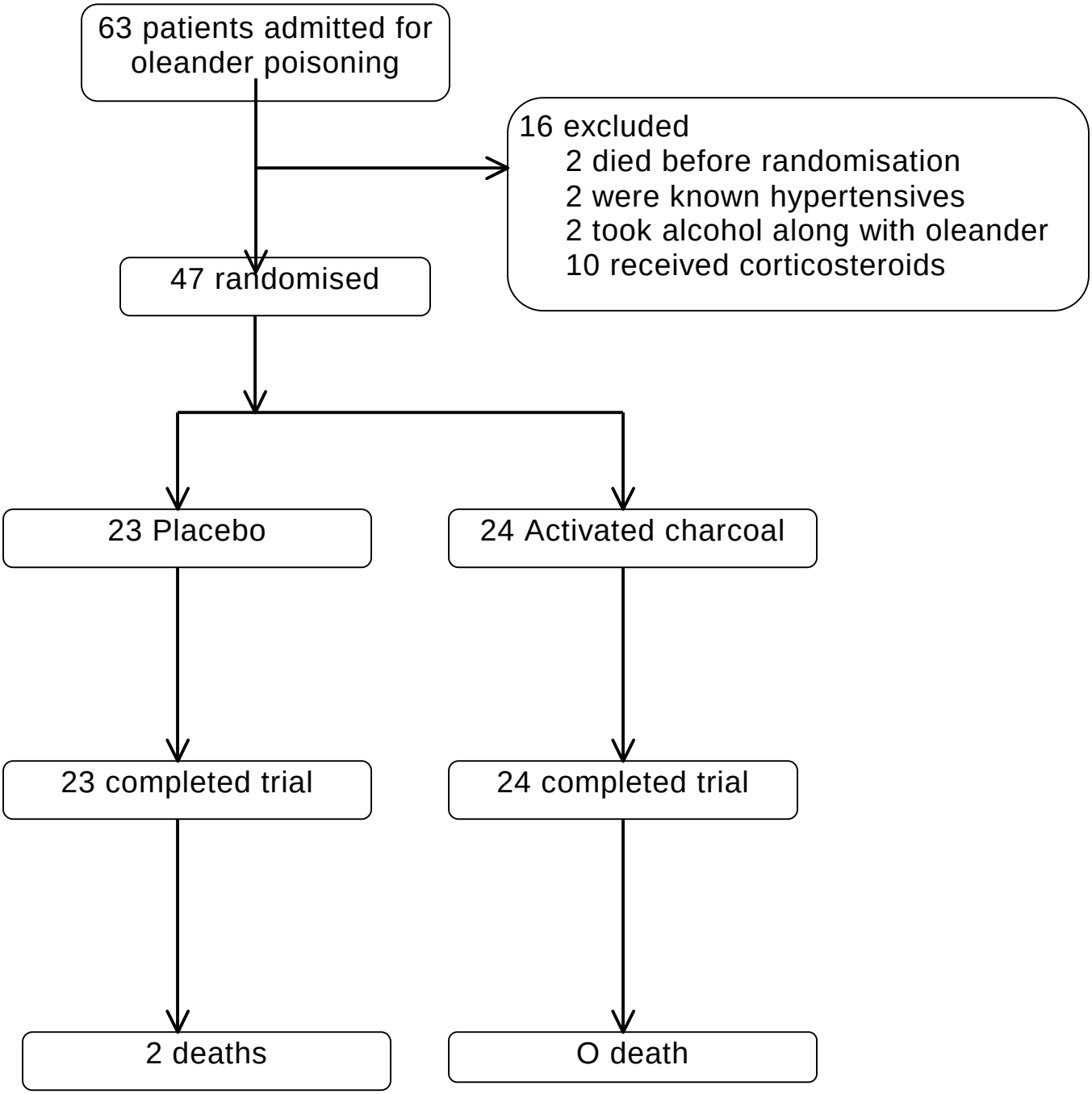
Death was used as primary end point. Patients were assessed for the frequency of life threatening cardiac arrhythmias (defined in this trial as second degree AV block type II, 2:1 second degree AV block, complete heart block, ventricular tachycardia, or any arrhythmia with hemodynamic compromise) or major cardiac arrhythmias (defined in this trial as life threatening arrhythmias as above plus any conduction disturbances of SA node or AV node or conducting system other than non-specific ST-T changes). The cardiac arrhythmias were assessed at presentation and monitored with serial ECGs.

Those with major or life threatening arrhythmias were treated with antiarrhythmic drugs including isoprenaline, lignocaine and amiodarone. None of the patients were treated with antidigoxin antibody fab fragments. Two patients received temporary pacing but both patients expired, one in the study group and one in the excluded group. No other patients in the study group received temporary pacing.

Doses of atropine used were calculated as well as the duration of hospital stay. Discharge criterion was sinus rhythm with rate greater than 60 per minute for 24 hours.

Patient's tolerance of charcoal by recording response to treatment was assessed. Bowel sounds were monitored regularly, and precautions were taken to help patients to avoid aspiration of activated charcoal, especially in those who received treatment via a nasogastric tube.

TRIAL PROFILE



TREATMENT PROTOCOL

1. Routine treatment after poisoning for ALL patients - gastric lavage, one dose of activated charcoal, IV access, cardiopulmonary resuscitation.

2. Randomly allocate patients into two sets who meet inclusion criteria.

Exclusion Criteria

- Who had taken another drug (alcohol, Organophosphates, Paracetamol etc)
- Coexistent diseases like DM/CVS disease/ hepatic or renal disease/ malignant disease.
- Those with severe infections.
- Pregnant and lactating women.
- Admitted after 24hrs of ingestion of poison.

3. One set of patients to receive 50gm activated charcoal dissolved in 400ml (2glasses) of water every 6hrs orally through nasogastric tube for three days.

    - Those who develop nausea/ vomiting → give Inj. metoclopramide 10mg IV.

4. Second set of patients to receive 400ml (2 glasses) of sterile water every 6hrs for three days

5. Other treatments/ Measures

    - Inj. atropine SOS (record the dose given)
    - Isoprenaline (record the dose given)
    - Do serum sodium, potassium, calcium, blood urea and serum creatinine
    - Do serial ECGs.
    - Look for life threatening cardiac arrhythmias and treat accordingly

6. Discharge criteria

- Sinus rhythm with rate greater than 60per minute for 24hrs.

STATISTICAL ANALYSIS

Statistical analysis was carried out for 47 subjects- 23 persons in the single dose activated charcoal and placebo group and 24 persons in the multiple dose charcoal group-after categorizing each variable.

Patient's age, sex, weight, no of seeds, seeds crushed or not, time taken after ingestion was matched. Other base line parameters like pulse rate, blood pressure, serum potassium level, serum sodium level, B. Urea, & S. Creatinine were analysed.

Occurrence of cardiac arrhythmias at presentation and at 24 hours after presentation, dose of atropine required, no of days for normalisation of ECG and duration of stay in hospital were evaluated& compared. Microsoft excel and SPSS (Statistical package for social sciences) were used for analysis and Z tests were done to assess differences between percentages and difference between means. Analysis was by intention to treat. Statistical significance was taken when $P<0.05$.

OBSERVATIONS

Table No 1

Matching of placebo & activated charcoal groups

	Placebo	Activated charcoal	P Value
Number	23	24	
Age (years)	25.74±7.75	26.75±10.11	0.69
Male Sex (%)	11 (47.82%)	11(45.83)	0.92
Height (cm)	156.48±11.83	158.83±9.32	0.42
Weight (kg)	54.65±8.76	56.21±8.65	0.55
Time after ingestion (hrs)	4.64±3.63	5.28±4.57	0.62
No of seeds	4.17±2.23	4.00±2.41	0.76
Seeds-crushed or Not Yes(%)	13 (56.52%)	19(79.16%)	0.09

Data are mean [SD] unless stated otherwise. P value less than 0.05 is considered statistically significant. Percentages are rounded off up to two decimals. SD means standard deviation.

Table No 2

Base line characteristics & biochemical parameters

	Placebo	**Activated charcoal**	**P Value**
Pulse rate (Per minute)	80.35±18.01	72.96±20.13	0.19
Respiratory rate (breaths/ minute)	17.74±1.84	18.00±2.83	0.68
Systolic BP (mm Hg)	110.61±11.03	114.43±14.19	0.32
Diastolic BP (mm Hg)	71.39±9.99	74.43±12.21	0.37
Serum Potassium (meq/L)	3.80±0.32	3.92±0.53	0.37
Serum Sodium (meq/L)	133.39±5.72	134.54±4.02	0.42
Serum creatinine (mg/dl)	0.95± 0.18	1.02±0.21	0.23
Blood Urea (mg/dl)	27.35±6.01	27.21±4.06	0.92

Data are mean (SD) unless stated otherwise. P value less than 0.05 is considered statistically significant. Percentages are rounded off up to two decimals. SD means standard deviation.

Table No – 3

Observations

	Placebo	**Activated charcoal**	**P-value.**
Mortality (%)	2(8.70%)	0(0%)	0.13
Life threatening cardiac arrhythmias at 0 hrs(%)	1(4.34%)	7(29.16%)	0.02
Major cardiac arrhythmias at 0 hours (%)	8(34.78%)	11 (45.83%)	0.42
Life threatening cardiac arrhythmias at 24 hours(%)	3(13.04%)	0(0%)	0.06
Major cardiac arrhythmias at 24 hrs(%)	7 (30.43%)	8(33.33%)	0.84
Number of days for normalisation of ECG	3.05±1.02	2.92±0.97	0.62
Dose of atropine required (in ampoules)	2.04±1.26	1.25±01.11	0.02
Days of stay in hospital	3.17±1.06	3.29±0.75	0.69

1 ampoule atropine =1.2mg atropine

Data are mean (SD) unless stated otherwise. P value less than 0.05 is considered statistically significant. Percentages are rounded off up to two decimals. SD means standard deviation

Table No 4

Stratified analysis of atropine requirement

	Placebo	**Activated charcoal**	**P value**
Dose of atropine required for patients presenting with life threatening cardiac arrhythmic at 0 hours (in no. of ampoules)	3± 0	2± 1.29	0.036
Dose of atropine required for patients presenting without life threatening cardiac arrhythmias at 0 hours (in no. of ampoules)	2± 1.27	0.94± 0.90	0.003

Data are mean (SD) unless stated otherwise. P value less than 0.05 is considered statistically significant. SD means standard deviation. 1 ampoule of atropine contains 1.2mg of atropine.

Between June 1, 2004 and may 31, 2005, 63 patients were admitted to IMCU and poison centre of Madras Medical College, Chennai with yellow oleander seed poisoning. Of these, 47 fulfilled entry criteria and were randomly allocated to a treatment group.

All patients in the study group completed the trial; all had normal heart rates at the time they left hospital. Discharge criterion was sinus rhythm with rate greater than 60 per minute for 24 hours.

Data from 47 patients participated in this study is finally entertained for analysis of which 23 patients belonged to placebo control group and 24 patients belonged to multiple dose activated charcoal group.

The cases and controls are matched for age, sex, weight, time after ingestion of seeds, number of oleander seeds consumed, and for whether they are crushed seeds or not, as shown in table number 1.

The cases and controls are age matched with a mean age of 26.75 (Standard deviation 10.11) and 25.74 (standard deviation 7.75) respectively. P value is 0.69 and hence not significant (P value>0.05).

Among the placebo plus single dose activated charcoal group 47.82% were males whereas in the multiple dose activated charcoal

group males were 45.83%. P value 0.92 (P value >0.05). Furthermore the slight difference in sex balance between the two groups is unlikely to have had an effect on cardiac complications of poisoning in such a young population.

Mean height of the patients in the cases was 158.83cm (Standard deviation 9.32) and in the control group 156.48 (Standard deviation 11.83). P value 0.42 (P value >0.05)

Weight of patients in the two arms of the trial were also matched, 54.65kg (standard deviation 8.76) and 56.21(standard deviation 8.65) in the control and cases respectively. P value 0.55 (P value >0.05).

Another important parameter that was taken into consideration for matching was the time elapsed after consumption of oleander seeds until presentation to hospital. In the control group mean time after ingestion of seeds was 4.64 hours (standard deviation 3.63) and in the cases group it was 5.28 hours (standard deviation 4.57) with a P value of 0.62. (P value> 0.05).

Time after ingestion of seeds varied from 45 minutes to as late as 16 hours in the control group and 45 minutes to 22 hours in the multiple dose groups. In the placebo group 73.9% of patients presented within 6 hours after consumption of seeds (see table No5) where as in the treatment group 75% presented within 6 hours.

Mean number of oleander seeds consumed in the control group was 4.17 with a standard deviation of 2.23, and in the cases, 4.00 with a standard deviation of 2.41. P value of 0.76 (P value >0.05). Although the median numbers of seeds ingested in the placebo and treatment group was 4.17 and 4.00 respectively, there was much variation in the number of seeds ingested. Two patients died in the placebo group took 3 seeds and 6 seeds respectively. Number of seeds taken varied from 1 seed to 8 seeds in the placebo group and 1 seed to 11 seeds in the treatment group (see table no 6)

Percentage of crushed seeds in the placebo group was 56.52% whereas in the treatment group 79.16%. p value 0.09. (p value >0.05)

Base line characteristics and biochemical parameters of the patients are shown in table number 2. Mean pulse rate 80.35 per minute (standard deviation 18.01) and 72.96 per minute (standard deviation 20.13); respiratory rate 17.74 per minute (Standard deviation 1.84) and 18.00 per minute (standard deviation 2.83); systolic blood pressure 110.61 mm of Hg (standard deviation 11.o3) and 114.43 mm of Hg (standard deviation 14.19); diastolic blood pressure71.39 mm of Hg (standard deviation 9.99) and 74.43 mm of Hg (standard deviation 12.21) were observed in the control and treatment group respectively. The P values were 0.10, 0.68, 0.32 and 0.37 respectively. (All P values > 0.05).

Mean serum potassium value in the control group was 3.8 meq/L (standard deviation 0.32) and in the charcoal group 3.92 meq/L (standard deviation 0.37). P value 0.37 (P value > 0.05) 87.2% of patients had normal serum potassium values, and 10.6% had hypokalemia. Contrary to general perception, only 1 patient (2.1%) had hyperkalemia. (see table no 7)

Other biochemical parameters like serum sodium, serum creatinine and blood urea were unremarkable except the fact that majority of the patients in both arms were mildly hyponatremic; a mean of 133.39 meq/L (control group) and 134.54 meq/L (treatment group) (see table No7)

Of the 63 patients admitted with oleander poisoning from June 1, 2004 to May 31,2005, 4 persons died of cardiac arrhythmias (a mortality rate of 6.35%). Of the 4 deaths, two deaths occurred within 3 hours of admission, and hence excluded from the study.

One of these two patients presented with complete heart block and later went for cardiac arrest. The other patient presented with ventricular tachycardia. Both these patients presented beyond 12 hours after consumption of oleander seeds and they took 5 seeds(crushed) and 3 seeds (not crushed) respectively. Pacing was attempted in the latter patient.

Among the study groups, there were two deaths (8.70%) in the placebo controlled group whereas there was no death (0%) in the

multiple dose group. But this reduction in mortality in the multiple dose arm was not statistically significant. P value 0.13. (P value >0.05). (See table No-3)

The first of these two patients died in the placebo controlled group consumed 3 crushed seeds and presented within 8 hours. Initial ECG showed sinus rhythm with non- specific ST-T changes only. 13 hours after admission she went for sudden cardiac arrest without any other major warning arrhythmias.

Second patient had taken 6 crushed seeds and presented within 7 hours of consumption and 13 hours later she went for cardiac arrest, preceded by ventricular tachycardia and multifocal atrial tachycardia. Pacing was tried in this patient also, but failed.

210 patients admitted with oleander poisoning in the poison centre and IMCU of Madras Medical College, Chennai, during the period between September 1, 2001 to May 31, 2004; with a mortality rate of 11.43%. Compared to that the mortality rate in the study group

was 4.25% (2 out of 47). This reduction in mortality was statistically just significant. P value 0.05.

Incidence of major cardiac arrhythmias at presentation was comparable in the both arms of the trial, 34.78% in the placebo group and 45.83% in the multiple dose group. P value 0.42 (P value>0.05) (see table No-3).

However the incidence of life threatening arrhythmias at presentation was more in the activated charcoal group (29.16%) compared to placebo group (4.34%). P value 0.02. (P value <0.05). This is statistically significant and may be a bias involved in allocation.

At presentation 29.8% had normal cardiac rhythm and 10.6% had sinus bradycardia. Non- specific ST-T changes were observed in 19.2% of patients. Most common major cardiac arrhythmia was first degree AV block (14.9%), followed by second degree AV block type I (6.4%); Second degree AV block type II was seen in 2.1% of patients.

Other arrhythmias observed were sinus arrest (2.1%), complete heart block (2.1%) and atrial flutter (2.1%). One patient (2.1%) had first degree AV block and junctional rhythm occurring intermittently in a single ECG strip. Another patient (2.1%) had complete heart block and junctional rhythm in a single strip. Intermittent atrial fibrillation and second degree AV block type II were observed in another patient (2.1%).

Of the 47 patients admitted 40.4% had major cardiac arrhythmias at presentation. One interesting observation is that all patients, presented after 12 hours of ingestion of oleander seeds had major cardiac arrhythmias (2 patients). Moreover two dead patients, excluded from the study, also presented more than 12 hours after consumption of seeds to hospital.

15 out of the 19 patients (78.95%) who had major cardiac arrhythmia at presentation consumed crushed oleander seeds whereas only 4 (21.05%) took it without crushing. It appears that cardiac arrhythmias are more if seeds are crushed, though this has to be verified with detailed statistical analysis.

Occurrence of major cardiac arrhythmias 24 hours after initial presentation was comparable in each arm, 30.43% in placebo arm and 33.33% in multiple dose arm. P value 0.84 (P value>0.05). There was a reduction in the occurrence of life threatening arrhythmias at 24 hours in the multiple dose arm, 0% Vs 13.04% in the placebo arm. But this reduction is not statistically significant. P value 0.06 (P value >0.05).

At 24 hours, 26.7% of patients had normal cardiac rhythm. Non-specific ST-T changes were observed in another 26.7%. 15.6% had sinus bradycardia. First degree AV block was the most common major cardiac arrhythmia at 24 hours, occurring in 24.4% of patients. Junctional rhythm was observed in 4.4% and second degree 2:1 AV block observed in 2.2% of patients. There was no case of atrial flutter / fibrillation or ventricular tachycardia at 24 hours.

Number of days taken for normalisation of ECG was almost equal in both groups, 3.05 days (standard deviation 1.02) in the

placebo group and 2.92 days (standard deviation 0.97) in the multiple dose group. P value 0.62 (P value > 0.05)

There was no significant reduction in the number of days of hospitalisation required either; 3.17days (standard deviation 1.06) and 3.29days (standard deviation 0.75) respectively. P value 0.69(P value>0.05).

But this study found statistically significant reduction in the dose of drug- atropine- needed in the multiple dose treatment group. Placebo group patients required a mean dose of 2.04 ampoules of atropine (standard deviation 1.26) where as multiple dose group needed a mean dose of 1.25 (standard deviation 1.11) ampoules only.(1 ampoule of atropine contains 1.2mg of atropine). This reduction has a P value of 0.02 and hence statistically significant. (P value<0.05)

Since there were significantly more number of life threatening arrhythmias in the multiple dose treatment group a stratified analysis

of the atropine requirement was carried out in patients presenting with life threatening cardiac arrhythmias and in those without.

There was statistically significant reduction in the dose of atropine required in the multiple dose arm, even though life threatening arrhythmias were much more in this arm; 2 ampoules (standard deviation 1.29) verses 3 ampoules in the single dose group. P value 0.036 (P value < 0.05).

This reduction in drug dose was more significant in patients presenting without life threatening cardiac arrhythmias; 2 ampoules (standard deviation 1.27) in the placebo controlled group and 0.94 ampoules (standard deviation 0.90) in the treatment group. P value 0.003 (P value <0.05).

7 patients who had severe nausea after starting the trial were given 10mg of intravenous metoclopramide. The most frequent adverse effects of treatment with multiple doses of activated charcoal were abdominal discomfort, vomiting and diarrhoea. 2 patients had

diarrhoea and 18 patients developed vomiting. The side effects were transient and resolved without any specific treatment.

Although most patients found the charcoal unpalatable, none refused to take it. Nine patients were given activated charcoal via a nasogastric tube. None developed aspiration or intestinal obstruction. No other complications were noted during the trial with the use of multiple dose activated charcoal.

Table No. 5

Time after ingestion of seeds at presentation

	0-6 hrs	**7-12 hrs**	**13-18 hrs**	**19-24 hrs**
Single dose (23)	17 (73.9%)	5 (21.7%)	1 (4.3%)	0
Multiple dose (24)	18 (75%)	5 (20.8%)	0	1 (4.2%)

Table No. 6

Number of seeds consumed

	1-2 seeds	**3-4 seeds**	**5-6 seeds**	**7-8 seeds**	**> 8 seeds**
Single Dose (23)	5 (21.7%)	11 (47.8%)	2 (8.7%)	5 (21.7%)	0
Multiple dose (24)	6 (25.0%)	10 (41.7%)	5 (20.8%)	2 (8.3%)	1 (4.2%)

Table No. 7

Serum Potassium level

	< 3.5 meq/L	**3.5 – 5.0 meq/L**	**> 5.0 meq/L**
Single dose (23)	3 (13.0%)	20 (87.0%)	0
Multiple dose (24)	2 (8.3%)	21 (87.5%)	1 (4.2%)

CHARTS & GRAPHS

Fig. 1

Age distribution

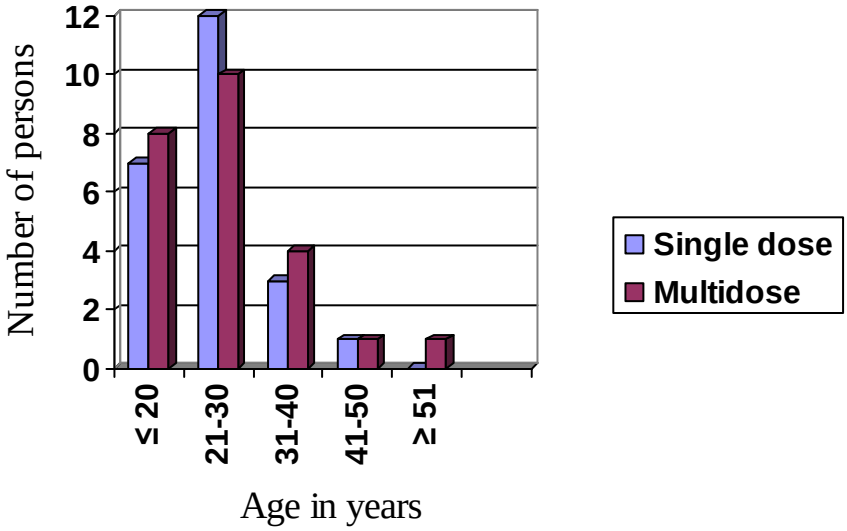


Fig. 2

Sex distribution

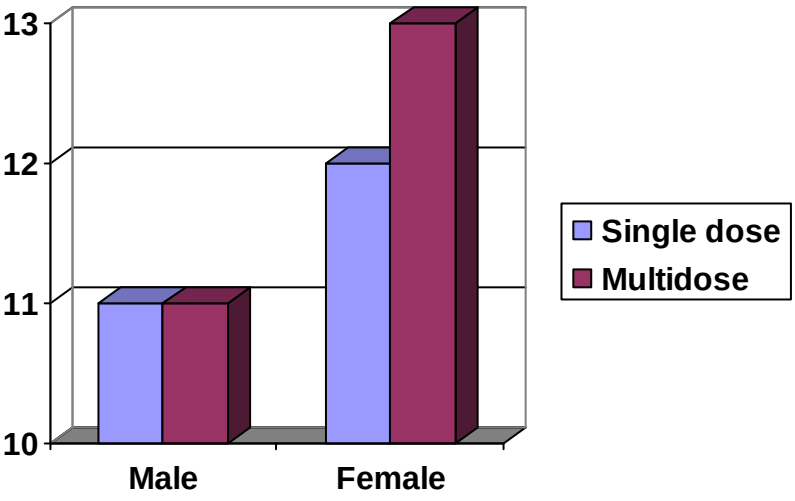


Fig. 3

Cardiac arrhythmias at presentation

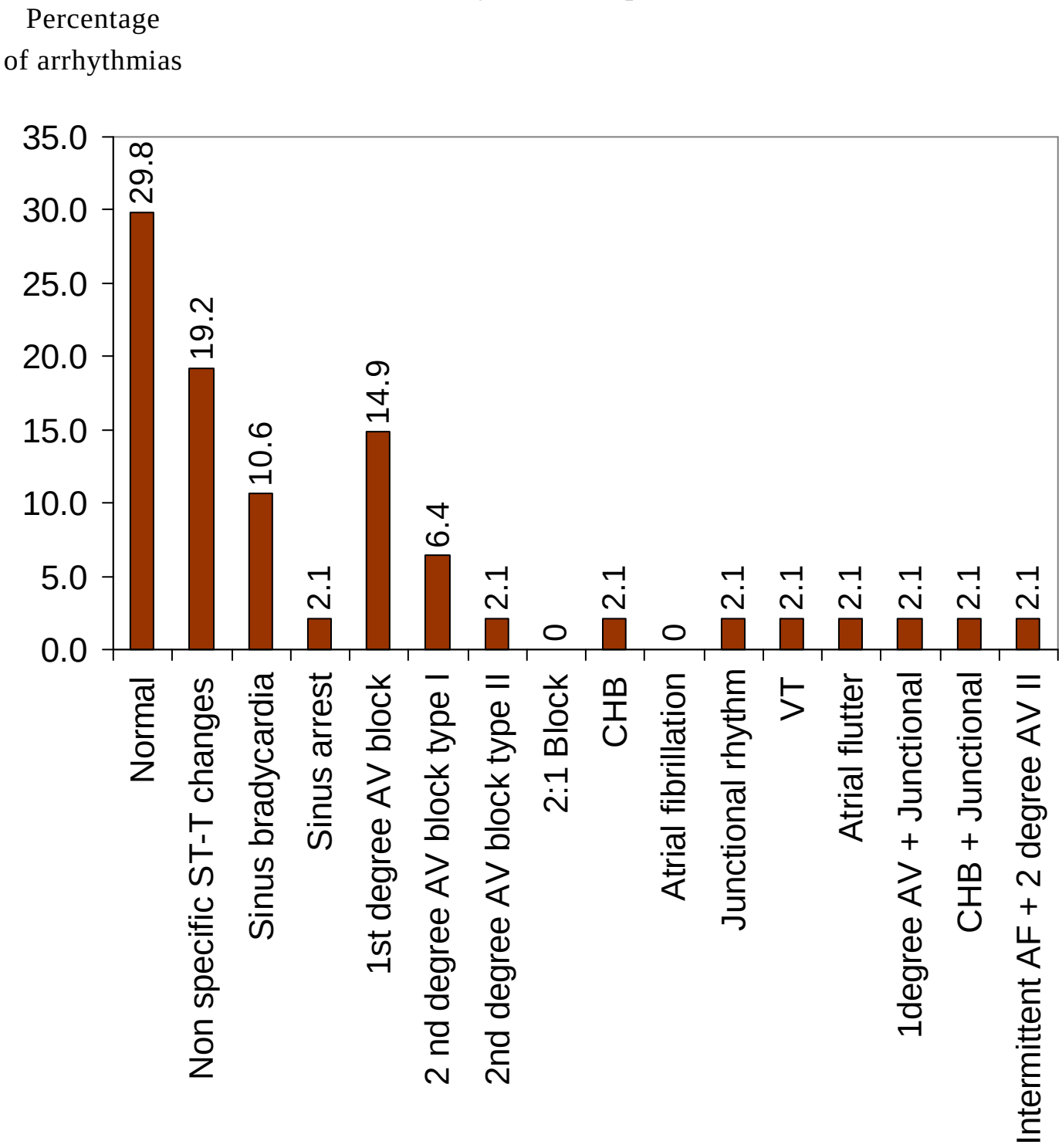
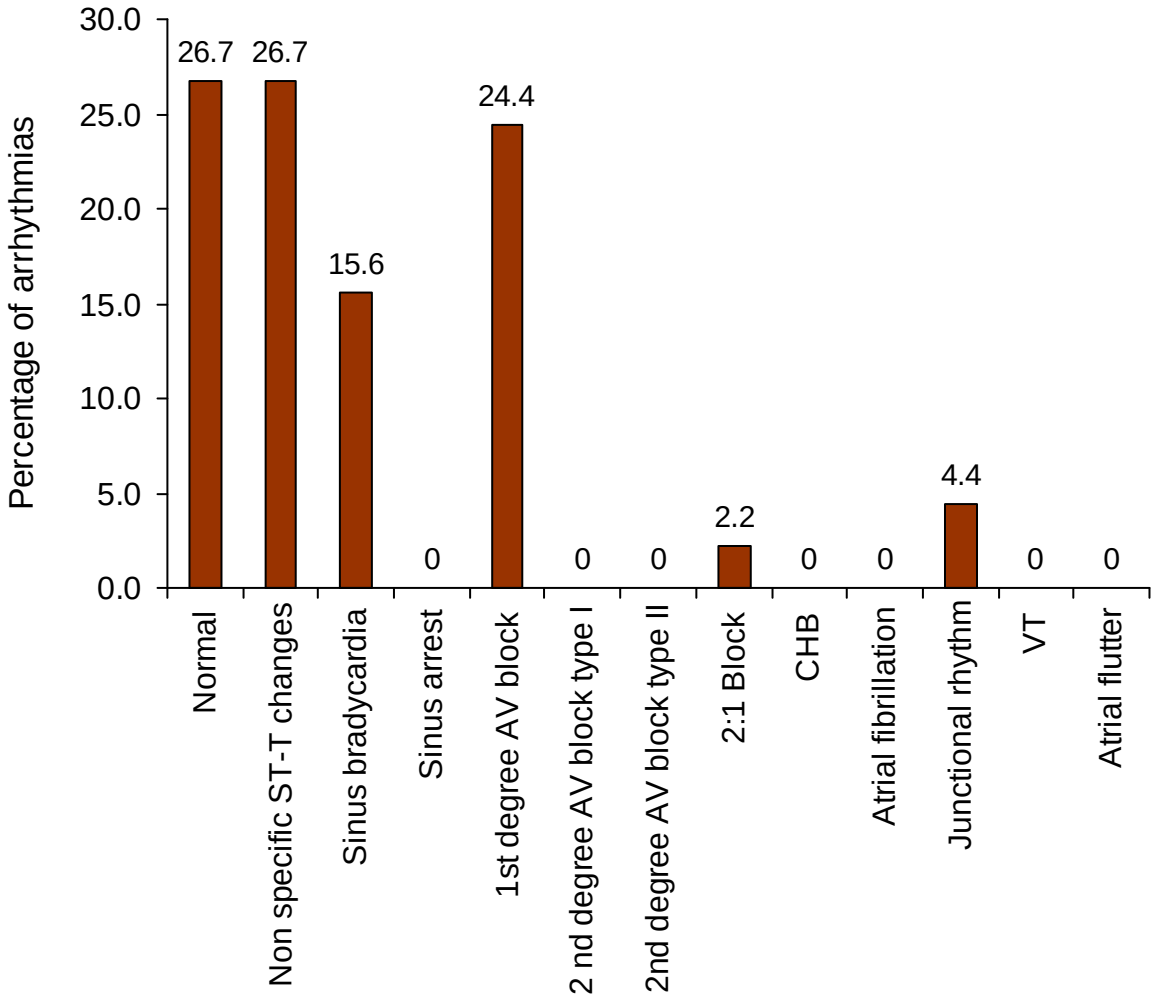


Fig. 4

`Cardiac arrhythmias at 24 hours



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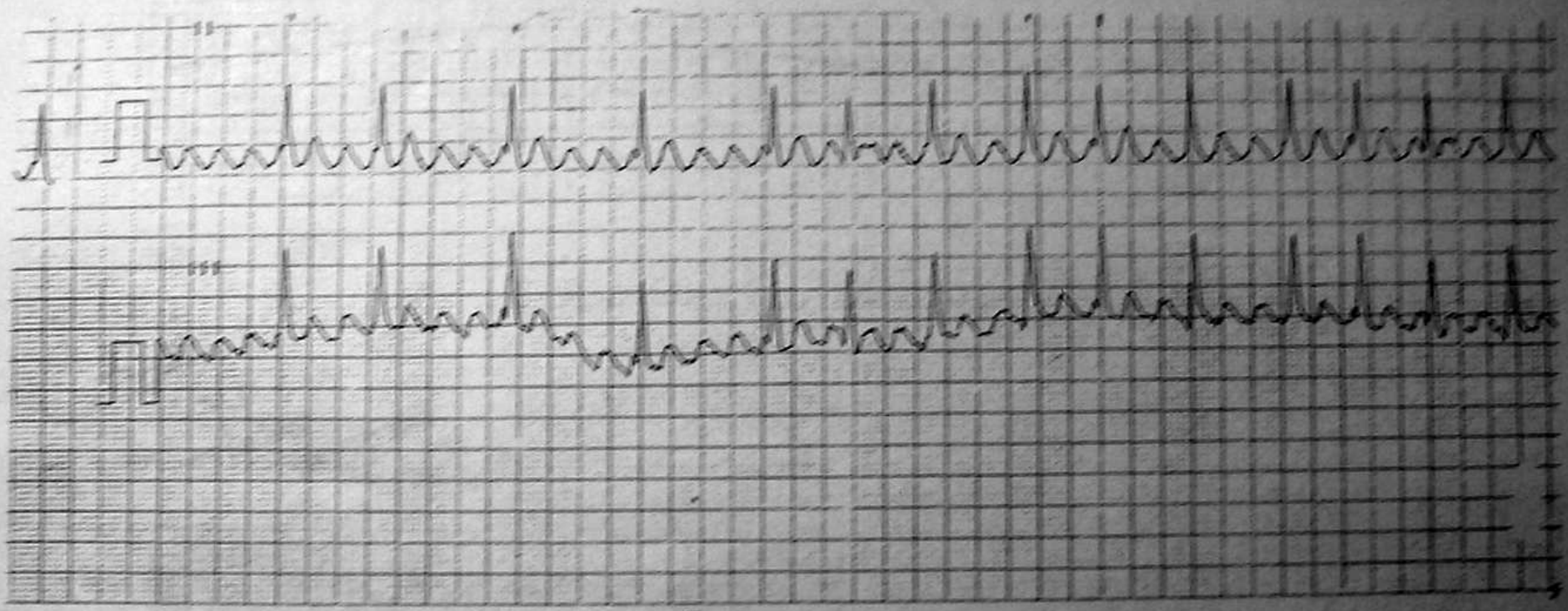

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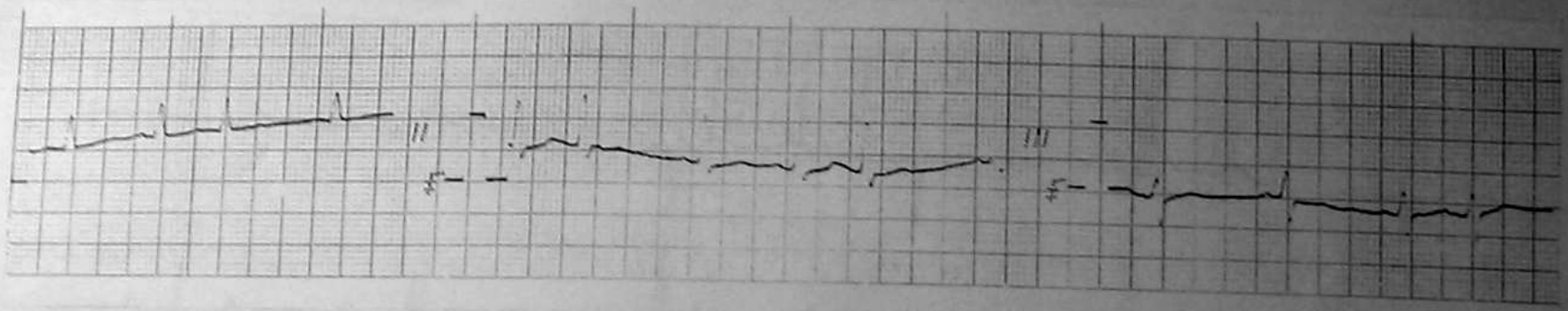

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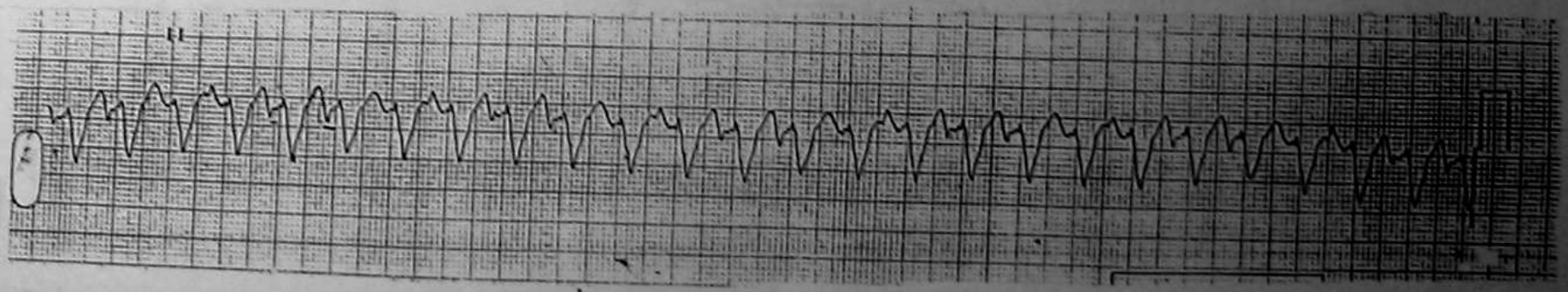

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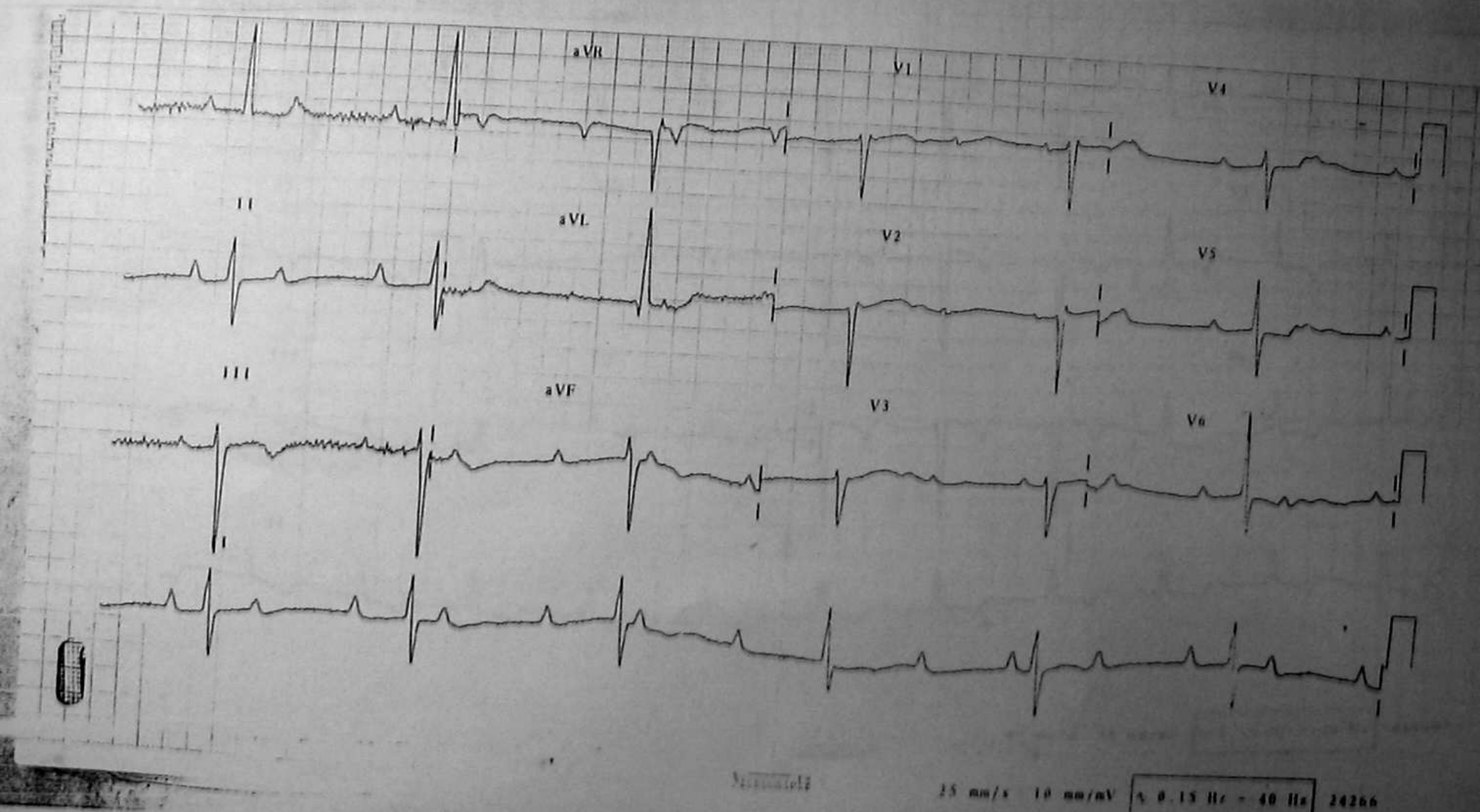

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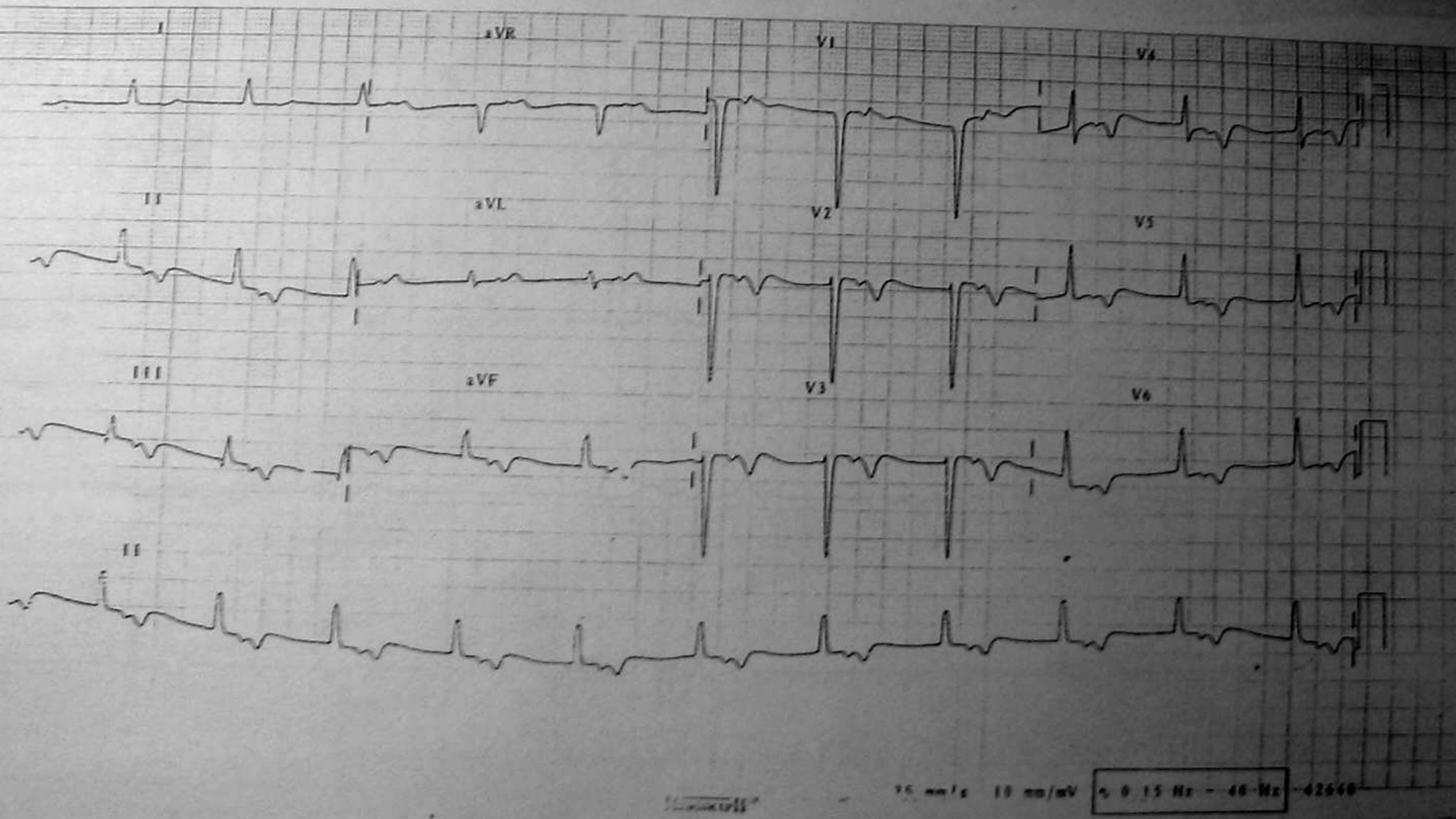

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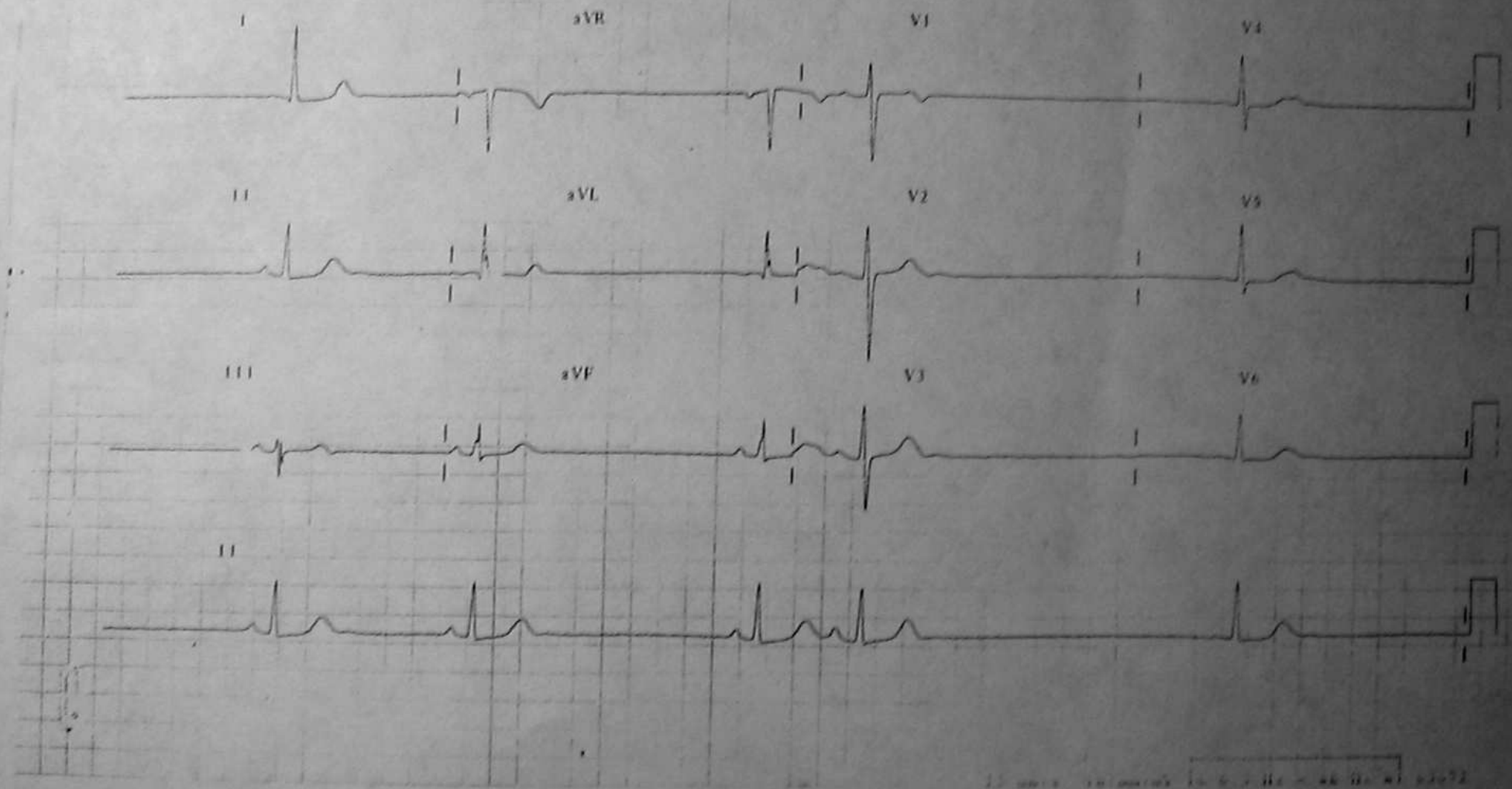

DISCUSSION

In this study of Indian population involving 47 patients, the aim was to assess the efficacy of multiple dose activated charcoal in the treatment of patients with yellow oleander poisoning.

Regarding base line parameters, the study showed no significant correlation with biochemical parameters like serum potassium, serum sodium or serum creatinine in the outcome of the patients in both arms of the trial. Most of the patients (87.2%) had normal potassium levels in serum and only 1 patient (2.1%) had hyperkalemia. This finding is in contrast to the study by Eddleston M, Ariaratnam et al[16]. where they reported hyperkalemia is very common in oleander seed poisoning.

According to the study by D.A. Warrel, Eddleston M et al most common cardiac arrhythmias in acute oleander poisoning were AV nodal and sinus nodal dysfunction, and ventricular arrhythmias were rare. In digoxin poisoning, the arrhythmia profile is different and ventricular ectopics and tachycardia are fairly common.

These observations are supported in this present study too. Most of the arrhythmias observed were of sinus node or AV node dysfunction and ventricular arrhythmias were extremely rare, both at initial presentation and after 24 hours. Only 2.1 percentage of patients had ventricular arrhythmias at presentation and none at 24 hours. Most common major cardiac arrhythmia both at presentation and 24 hours after initial presentation was first degree AV block.

According to similar trial done by H.A. De Silva et al[21] in Sri Lanka, 2002, there was 69% reduction in death rate when multiple dose charcoal was used, compared with a placebo. They also found significant reduction in the occurrence of major arrhythmias at 24 hours and in the doses of atropine in the multiple dose treatment arm.

However in the present study, though there was a reduction in mortality in the multiple dose arm; zero verses two; this was not statistically significant. This could be due to smaller sample size in this study. Moreover most of the patients presented with life threatening arrhythmias were allocated to the multiple dose treatment

arm. This would have further decreased mortality, in the placebo controlled arm.

Another interesting finding was that the poison centre and IMCU of Madras Medical College had a mortality rate of 11.43 percentage among 210 patients admitted between September 1, 2001 to May 31, 2004. In the current study which included 47 patients admitted from June 1, 2004 to May 31, 2005 the mortality rate was only 4.25%. This is statistically just significant.

This reduction in mortality could be attributed to the use of multiple dose activated charcoal in over half of these patients. Again its noteworthy here that most of the patients with life threatening arrhythmias at presentation received multiple dose activated charcoal.

Occurrence of major cardiac arrhythmias 24 hours after initial presentation was comparable in both arms of the trial. But there was reduction in the occurrence of life threatening cardiac arrhythmias at 24 hours in the multiple dose activated charcoal treatment arm; zero

percentage verses 13.04 percentage in the placebo arm. But this reduction is not statistically significant.

In the study by H.A. de Silva et al[21], there was significant reduction in occurrence of life threatening cardiac arrhythmias at 24 hours in the multiple dose group. The smaller sample size in the current study may be the cause for the statistical insignificance.

Number of days taken for normalisation of ECG was comparable in both arms of the trial. Also there was no significant reduction in the number of days of hospitalisation required. The Sri Lankan study by H.A. de Silva also showed similar results.

The current study found statistically significant reduction in the dose of drug atropine needed in the multiple dose treatment group. Since there was significantly more number of life threatening arrhythmias in the multiple dose treatment group, a stratified analysis of the atropine requirement was carried out in patients presenting with life threatening cardiac arrhythmias and in those without.

There was statistically significant reduction in the dose of atropine required in the multiple dose arm, even though life-threatening arrhythmias were more in this arm. This reduction in drug dose was more significant in patients presenting without life threatening arrhythmias.

The need for early treatment to prevent death after poisoning with yellow oleander is emphasised by the fact that all the deaths during the study period occurred within 13 hours of admission. Also all the patients presented more than 12 hours after consumption of oleander seeds had major cardiac arrhythmias.

Furthermore, some of the patients had sudden cardiac events causing death; that were not preceded by arrhythmias suggestive of the need for temporary cardiac pacing or antidigoxin antibody fab fragments. All patients in our study were treated within 24 hours of poisoning.

In this study activated charcoal was found to have been tolerated well and had no serious side effects. It is noteworthy that in yellow

oleander poisoning, activated charcoal acts not only through prevention of the initial absorption of the toxic glycosides, but also by preventing toxin reabsorbtion after intestinal secretion from the systemic circulation.

The effectiveness of activated charcoal in reducing the severity of yellow oleander poisoning is lent support by the fact that the dose of atropine required in the multiple dose arm was much lower, even though this arm included majority of the patients with life threatening cardiac arrhythmias at presentation.

However, current study could not show statistically significant reduction in mortality and occurrence of life threatening cardiac events at 24 hours after admission, in the activated charcoal treated group. A larger sample size is required to confirm this conclusion.

In our country, patients from rural areas who need temporary cardiac pacing for life threatening bradyarrhythmias after yellow oleander poisoning are usually transferred to a tertiary care centre.

Such transfers and cardiac pacing are costly and have resulted in deaths during transit.

Treatment with anti-digoxin antibody fab fragments is very expensive and not widely available. And some of the patients may require more than one dose. Thus there is a pressing need for an inexpensive and effective treatment that can be used in non-urban hospitals. Activated charcoal is easily available and inexpensive.

Multiple dose activated charcoal is safe and effective and should be given to all patients who have ingested yellow oleander seeds. Expensive interventions such as cardiac pacing and anti-digoxin antibody fab fragments could be reserved for patients who have dangerous arrhythmias at the time of presentation with oleander poisoning or those who develop arrhythmias despite treatment with activated charcoal.

It is probable that the multiple dose activated charcoal could also be of use in the treatment of patients who have been poisoned

with other cardiac glycosides. A previous study in 23 patients[25] and a few anecdotal reports[26] have shown that charcoal increases the clearance rate of digoxin, and experimental evidence shows much the same effect on digitoxin clearance.[26]

CONCLUSION

The following are conclusions from the study

1. Multiple dose activated charcoal is safe and effective in the treatment of oleander seed poisoning and it reduced the atropine requirement significantly.

2. It is effective in reducing death and life threatening cardiac arrhythmias in oleander seed poisoning. But this reduction is not statistically significant. This impression in this study may be due to smaller sample size.

3. There was no reduction in the number of days of stay in the hospital or in the number of days taken for normalisation of ECG.

SCOPE FOR FUTURE STUDIES

1. As already stated, the reduction in mortality and life threatening cardiac arrhythmias by multiple dose activated charcoal in the treatment of oleander seed poisoning has to be verified with a larger sample size.

2. Multiple dose activated charcoal could also be of use in patients who have been poisoned with other cardiac glycosides like digoxin, odollam (cerbera odollam) etc. Odollum poisoning is very common in south India, whose active principle is cerberin (thevetin-B), which is same as that contained in yellow oleander. So activated charcoal may have a potent role in the treatment of odollum poisoning.

3. As the oleander seeds produce a toxic carditis like picture many cardiologists advise anti inflammatory agents like corticosteroids. At the poison centre of our hospital, as advised

by cardiologist, 10 patients received corticosteroids during the study period. These patients were excluded from this study. To evaluate the role of steroids in oleander seed poisoning, further studies are required.

PROFORMA

Name:	Age:	Sex:	IP No:
Height:	Weight:	Unit:	DOA:

1. Time after ingestion :
2. Number of seeds :
3. Pulse rate :
4. Respiratory rate :
5. Blood pressure :
6. Serum Potassium :
   - Sodium :
   - Creatinine :
   - Calcium :
   - Blood urea :
7. Dose of atropine given (total) :
8. Dose of isoprenaline given (total) :
9. ECG
   - Day 1 :
   - Day 2 :
   - Day 3 :

S. No	Name	Age	Sex	Ht	Wt	Time	Seed no.	Crushed	PR	RR	SBP	DBP	K	Na	Cr	Urea	Life ECG 0 hrs	Major ECG 0 hrs	Life ECG 24 hrs	Major ECG 24 hrs	Normal ECG days	Drug	Stay
1	Yuvaraj	20	M	165	65	1	8	N	86	18	110	70	3.2	133	0.8	20	N	N	N	N	4	4	4
2	Ramesh	27	M	117	68	4	3	Y	100	16	100	70	3.8	136	1.3	26	N	Y	N	Y	4	4	5
3	Vartha	24	F	150	46	1	5	N	90	20	110	80	3.9	136	1.1	32	N	N	N	N	1	0	3
4	Murugan	23	M	164	54	4	4	Y	100	16	100	80	3.6	140	0.7	18	N	N	N	N	3	1	4
5	Ramachandran	45	M	168	65	1	2	N	80	16	130	80	4.6	128	0.9	34	N	N	N	N	1	0	3
6	Sheela	26	F	148	52	8	4	Y	68	22	130	70	3.7	131	0.9	20	N	Y	N	Y	4	3	4
7	Gowrinathan	39	M	162	55	6	6	Y	90	16	120	80	3.8	133	0.9	36	N	N	Y	Y	4	3	4
8	Sadasivam	30	M	172	70	7	3	Y	92	16	100	60	3.5	138	0.9	35	N	N	N	N	3	2	3
9	Komathy	30	F	156	50	16	3	N	56	16	110	70	3.4	135	0.9	26	N	Y	N	N	3	2	3
10	Muthalagu	34	M	170	72	0.75	3	Y	108	20	120	80	4.4	116	1.0	30	N	N	N	N	3	2	3
11	Prakash	21	M	168	54	4	3	Y	62	16	100	70	3.8	136	0.9	30	N	N	N	N	3	2	3
12	Janaki	22	F	162	53	9.5	4	Y	60	16	110	70	3.9	132	0.6	36	N	Y	N	Y	3	3	3
13	Shanmugam	20	M	166	57	4	8	Y	86	16	130	80	3.2	130	0.8	20	N	N	N	N	4	3	3
14	Vruthambal	15	F	148	44	8	3	Y	64	18	110	80	4.1	136	0.7	18	N	N	expired	-	-	1	.5
15	Selvi	36	F	154	58	6	7	Y	70	20	110	70	3.7	130	0.9	26	N	Y	expired	-	-	4	.5
16	Poongavanam	28	F	152	54	1.5	2	N	84	18	116	74	3.6	128	0.9	22	N	N	N	N	1	0	3
17	Valliammal	29	F	155	50	2.5	2	Y	96	18	110	60	3.7	130	1.1	26	N	N	N	N	3	1	3
18	Kamala	30	F	148	48	5	2	Y	60	18	100	70	4.0	134	1.3	30	N	Y	N	Y	4	2	4
19	Seshadri	24	M	165	60	1	8	N	50	20	110	70	3.9	140	1.1	22	N	N	N	N	2	1	2
20	Manimegalai	16	F	154	42	3.5	3	N	56	20	96	60	3.7	130	1.0	26	N	Y	N	Y	4	3	4
21	Renuka	17	F	150	48	7	4	N	88	18	100	70	3.9	134	1.1	32	N	N	N	N	4	2	4
22	Balaji	16	M	160	52	1	1	N	90	16	126	88	3.9	136	1.1	36	N	N	N	N	3	1	3
23	Yasodha	20	F	145	40	5	8	N	112	18	96	40	4.0	146	1.0	28	Y	Y	N	Y	3	3	4

Single dose charcoal

S.No	Name	Age	Sex	Ht	Wt	Time	Seed no.	Crushed	PR	RR	SBP	DBP	K	Na	Cr	Urea	Life ECG 0 hrs	Major ECG 0 hrs	Life ECG 24 hrs	Major ECG 24 hrs	Normal ECG days	Drug	Days stayed
1	Sarangapani	45	M	168	64	3	3	Y	52	16	140	100	4.1	136	1.1	24	N	N	N	N	2	3	2
2	Karthik	14	M	156	46	6	1	Y	48	16	100	70	4.3	140	0.9	24	N	N	N	Y	4	2	4
3	Prakasham	55	M	171	65	1.5	3	Y	72	16	110	90	3.9	140	0.9	28	N	N	N	N	4	1	4
4	Rajendran	39	M	168	70	22	7	Y	76	18	120	70	4.1	139	1.2	32	N	Y	N	Y	3	0	3
5	Gangamma	27	F	152	53	1	2	Y	54	16	100	70	3.6	136	1.3	28	N	Y	N	N	4	1	4
6	Anandhi	35	F	154	60	5	3	Y	84	18	120	80	2.4	138	0.8	25	N	N	N	N	1	0	3
7	Geetha	29	F	150	58	11	2	Y	80	18	140	80	3.2	138	0.8	24	N	N	N	N	3	1	3
8	Saravanakumar	20	M	171	66	4	1	N	80	20	100	70	3.8	134	1.0	26	N	N	N	N	2	0	2
9	Girija	15	F	144	44	1	5	N	110	16	120	70	3.6	128	0.7	23	N	N	N	N	2	1	3
10	Jayanthi	22	F	154	51	0.75	2	Y	90	18	110	70	4.1	130	1.1	30	N	N	N	N	1	0	2
11	Kannan	26	M	174	71	6	3	Y	90	16	116	80	4.3	138	1.3	34	N	Y	N	Y	3	1	3
12	Kandan	38	M	168	62	2	4	N	52	18	130	86	3.9	132	1.2	30	N	N	N	N	3	2	4
13	Kannan	17	M	164	50	3	4	Y	80	16	110	70	3.7	132	1.1	32	N	N	N	N	3	0	3
14	Selvi	28	F	156	54	6	1	Y	90	18	110	80	4.3	133	1.1	22	N	N	N	N	3	1	3
15	Sumathi	20	F	154	48	3	8	N	66	16	114	70	4	136	1.0	29	N	Y	N	Y	3	2	3
16	Srinivasan	25	M	170	66	8	3	Y	100	20	140	90	4.6	138	1.1	34	N	N	N	N	3	1	3
17	Seetha	17	F	150	48	2	3	Y	96	18	116	70	3.8	140	0.9	24	N	N	N	N	3	0	3
18	Amutha valli	29	F	150	48	4	6	Y	?	12	?	?	3.7	134	1.6	28	Y	Y	N	Y	3	1	4
19	Kumar	25	M	172	70	9	11	N	80	20	96	60	4.1	130	0.9	32	Y	Y	N	N	2	1	4
20	Porkodi	18	F	146	46	3	4	Y	44	16	110	70	4.2	130	0.8	30	Y	Y	N	N	5	4	5
21	Kalaiselvi	23	F	152	54	10	6	Y	54	22	100	60	5.3	138	0.8	26	Y	Y	N	Y	3	3	3
22	Mahesh	19	M	162	48	4.5	3	Y	58	20	110	50	3.8	131	0.8	24	Y	Y	N	Y	4	3	4
23	Prema	21	F	156	51	4	5	Y	88	26	130	96	3.9	130	1.1	18	Y	Y	N	N	4	1	4
24	Vasantha	35	F	150	56	7	6	Y	34	22	90	60	3.3	128	1.0	26	Y	Y	N	Y	2	1	3

Multiple dose charcoal

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