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Evaluation of Cardioprotective action of *Suvarna gairik* (Redochre) in Indian Cobra Envenomation, Aluminium Phosphide Poisoning and Doxorubicin Cardiotoxicity in Albino Rats- A Protocol

Santoshi Mane [a,b*#†], Nilima Wadnerwar [a‡], Sudhir Ninave [c†], R. D. Wajgi [d≡] and R. R. Dighade [e¥]

[a] Department of Agadtantra, Mahatma Gandhi Ayurved College Hospital and Research Centre, Salod [Hirapur], Datta Meghe Institute of Medical Sciences [Deemed to be University], Wardha, India.
[b] Department of Agadtantra, L.R.P. Ayurvedic Medical College, Islampur, Dist-Sangli, Maharashtra, India.
[c] Department of Forensic Medicine and Toxicology, Jawaharlal Nehru Medical College, Sawangi (M), Datta Meghe Institute of Medical Sciences [Deemed to be University], Wardha. India.
[d] Yeshwantrao Chavan College of Engineering, Nagpur, India.
[e] Yeshwantrao Chavan College of Engineering, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: Poisoning is major health issue all over the world. Poisoning is one of basic causes for Out Hospital cardiac arrest (OHCA). P-OHCA (Poison induced Out Hospital cardiac arrest) can be prevented by immediate primary management. The agent for poisoning is unknown in most cases, which leads to difficulty deciding the emergency antidote. In Ayurveda *Hridyavaranchikitsa* (Cardio protection) is one of the treatment modalities mentioned in all types of poisoning as first aid

[#] PhD Scholar;
[†] Professor and Head;
[‡] HOD & Associate Professor;
[≡] Assistant Professor;
[¥] Associate Professor
**Corresponding author: E-mail: drsantoshimane@gmail.com;*

treatment. *Suvarna Gairik* (Red ochre) is one of drugs mentioned for the cardioprotection. Snake bite and organophosphate poisoning are the threats to life in India. Doxorubicin is commonly used drug for Chemotherapy in malignancies, and its major side effect is cardiotoxicity. Hence these poisonings are included in study.

Aim and Objective: Evaluation of cardioprotective activity of *Suvarna Gairik* (Red ochre) in cardiac biomarker like Lactate dehydrogenase, Creatinine phosphokinase, Alkaline transferase, Cardiac Troponins and Survival Time in Indian Cobra Envenomation, Aluminium phosphide poisoning and Doxorubicin cardiotoxicity in Albino Rats.

Methodology: Animal study is designed. 56 wistar rats will be divided in 7 groups as Vehicle Control Group, Disease control Group -1 Indian Cobra envenomation, Disease control Group -2Aluminium Phosphide poisoning, Disease control Group -3 Inj. Doxorubicin induced cardiotoxicity, Test Group -1 Indian Cobra Envenomation and *Suvarna gairik* Test Group -2 Aluminium Phosphide poisoning and *Suvarna gairik* Test control Group 3- Inj. Doxorubicin cardiotoxicity and *Suvarna gairik.*

Results: Outcome will be assessed in between groups and among groups.

Conclusion: *Suvarna Gairik* (Red ochre) may show statistical significant cardioprotective activity.

Keywords: Cardioprotective action; hridyavaranchikitsa; Suvarna gairik (Red ochre); Indian cobra envenomation; aluminium phosphide; doxorubicin cardiotoxicity.

1. INTRODUCTION

Poisoning intentionally or accidentally is being major health issue globally and it became fateful.1,93,460 death occurs worldwide due to unintentional poisoning in 2012 [1]. Worldwide various agents such as agrochemical compounds, drugs or environmental agents; gases etc intentionally or unintentionally are used as poisoning agents. Even medicines used for therapeutic purposes can cause adverse effects or poisonous effect. In India mortality rate due to poisoning varies around 20% [2]. Acute poisoning is medical emergency and needs earlier and effective primary intervention. It may decrease the mortality and complication due to poisoning. Timely initiation of medical management at primary level can save the life in poisoning cases.

Out-of-hospital cardiac arrest (OHCA) is increasing health issue. 55 adults per 100,000 person per years go through OHCA. Incidence of OHCAs with non-cardiac origin is 28% in an Asian countries.OHCAs can occur due to other than cardiac causes and one major non cardiac origin cause of it is poisoning. Poisoning-induced out-of-hospital cardiac arrest (P-OHCA) can be lowered by using immediate preventive measures and first aid treatment in poisoning [3].

Toxicology is being updated with continuous research and advanced techniques are introduced for diagnosis and estimation of poisons and use of specific antidotes. But to reduce mortality rate there is need to use integrated treatment modalities in emergency condition in poisoning. Agadtantra (Ayurvedic Toxicology) is one of the eight branches of Ayurveda [4]. In agadtantra many agadas (Ayurvedic antidotes), vishghana dravyas are mentioned. *Acharya Charak* has mentioned 24 treatment modalities for poisoning in *Ayurveda.*One of the treatment modalities is *Hridyavaran* (cardioprotection). *Hridyavaran* is the treatment mentioned in all types of poisoning as first aid treatment. *Hridyavaran* means *hridya rakshkaraushadham* (cardioprotection) [5]. *Acharya Charak* [6] *Acharya Sushrut* [7] and *Aacharya Vagbhat* [8] have mentioned that in any type of poisoning *Hridyavaran* (cardioprotection) of poisoned patient should be done with priority. Many drugs are mentioned for cardioprotection. *Aacharya Charak*has mentioned *Madhu*(honey), *Sarpi/Ghruta*(Ghee), *Majja*, *Paya*(Cow milk), *Suvarna Gairika* (Red Ochre, anhydrous Fe2O3), *Gomayrasa* (water separated from cow dung), sugarcane juice, crow meat soup, fresh blood of goat, cow dung ash, black mitti (soil) should be given to *vishakta rogi* (poisoned patient) as early as possible to protect his/her heart [9]. In modern medicine cardiopulmonary resuscitation is described as first principle of general line of treatment of the poisoning. With priority ABCD treatment of emergency resuscitation should be done to stabilize the vitals of poisoned patient and then next measures can be done to neutralize the poison. So to reduce mortality rate in tertiary care hospitals or in remote areas due to poisoning the integrated therapy in the first aid treatment should be adopted. Alternative medicine from Ayurveda with contemporary medicine may be beneficial to reduce the mortality rate in poisoning. Ifdue to *Hridyavaran*

chikitsa (cardioprotection) survival time is increased then it can be useful to give enough time to attain pharmacological action of specific antidotes.

Venomous snake-bite causes fatal outcomes and many health complications. Proper treatment strategies required for snake bite. Many cases of snake are not documented and cannot obtain actual data, but still it is estimated that 5 million snake-bites occur each year, resulting in up to 2.5 million envenoming, at least 100,000 deaths occurs and also needs many other permanent disabilities [10]. India is agricultural country and due to occupational hazards snake bite occurs in high amount which results many deaths.Cardiac toxicity is a well defined complication of poisonous snake bite. Among the four deadly venomous snakes, Indian cobra is neurotoxic snake. The cobra venom potency causing myocardial toxicity is 1/20 of its neurotoxin. The action of cobra venom is directly seen on cell membrane causing many effects on the skeletal, smooth muscles like cardiac muscles, nerves and neuromuscular junction, thus causing to cardiovascular collapse and respiratory paralysis. The neurotoxin and carditoxins of elapid snakes carry strong positive charge, resulting in rapid lethal absorption. Cobra venom cardiotoxin causes cell depolarization, resulting in hypotension and even death. Unless the right antivenin is administered shortly, the cobra bite victim can die within 30 minutes. So in this study Indian Cobra Envenomation is included.

India is agricultural country. Increasing demand of food and agricultural development causes excess use of pesticides. As it is easily available source it si mostly used for intentional poisoning. 370,000 deaths occur due to deliberate ingestion of pesticides each year [11]. It may be because insecticides and pesticides are easily available and accessible in Indian market, including rural and urban areas, and so used to commit suicide. Aliuminium phosphide is easily available in the market and highly toxic fumigant and commonly used as pesticide for grain preservation. It's also known as Rice tablet and its use is widely increased due to its wide availability, high efficacy against different pests, low cost and safe decomposition product which are considered to be environmentally safe. But nowadays mostly it is intentionally used for poisoning [12]. So in this study Aluminium phosphide has been taken. Myocardial injury associated with Aluminium phosphide is noted.

Drug toxicity is an upcoming major health problems in this era. Doxorubicin is one of the chemotherapy drugs used in malignancies. It is observed that it causes cardio toxicity, due to which its use is limited. Doxorubicin causes heart damage and it develops the cardiomyopathy. It leads to a poor prognosis which is frequently fatal. Doxorubicin induced cardiomyopathy is treated with the presently available treatment for established cardiomyopathy but it does not appear to improve prognosis [13]. Extensive research has been done but there is need to find out effective and clinically applicable preventive measures.

Suvarna Gairk (Red ocher) is one of the drug specified for cardioprotection in all types of poisoning. According to Ayurveda *Suvarna Gairika* has the cardioprotective property in poisoning. The objective of the present study is substantiation of cardioprotective action of *Suvarna Gairik* (Red ochre) in Indian Cobra Envenomation , Aluminium phosphide poisoning and Doxorubicin cardiotoxicity in Albino wistar rats in respect to Cardiac Biomarkers like Lactate dehydrogenase, Creatinine phosphokinase, Alkaline transferase, Cardiac Troponins and Survival Time and Survival Rate.

2. MATERIALS AND METHODS

Total 56 Albino Wistar rats will be procured for animal study. Albino Wistar rats of either Sex Male and Female, of age- 12 weeks, of weight 200- 250 gm and healthy will be used. Unhealthy rats, weight below 200.0 gm and above 250 gm will be excluded from study. For identification coding of animal will be done. By simple randomization method animals will be divided in groups. Principal investigator/Research scholar will be aware of the group allocation at the different stages of the experiment. All other will be blinded for the study. The results will be measured in terms of Survival Time, Survival Rate, Cardiac Biomarker, Lactate dehydrogenase, Creatinine phosphokinase, Alkaline transferase (ALP), Cardiac Troponins, Haematology Criteria, Biochemistry Criteria and Histopathology observation of Heart, Aorta, Liver. Survival time will be the primary outcome measure. ANALYSIS OF VARIANCE, POST HOC TEST, Krushall Wallis Test for qualitative data measurements will be applied.

Housing and husbandry: Albino Rats will be kept under observation before experiment for acclimatization.RO water in ad libitum is provided with sterile food pallets. Day and Night cycle of 12:12 will be followed. Room temperature would be in between 18-29 degree and humidity 30-

70%.Proper precautions will be taken in the experimental protocols to reduce pain, suffering and distress.

2.1 Experimental Procedures

Group I Vehicle Control Group (VC) Albino wistar rats will be given plain water.

Group II Disease control Group -1 (DC-1) Indian Cobra Envenomation will be induced by administering Indian Cobra venom 0.216 mg.IM once Followed by Inj PVASV 0.36 ml IV once.

Group III Disease control Group -2 (DC-2) Aluminium Phosphide poisoning will be induced by administering Aluminium Phosphide tab 2.7 mg orally once with water.

Group IV Disease control Group -3 (DC-3) Inj. Doxorubicin 2.5 mg /kg body weight in 6 equal injections alternatively for two weeks to make a total cumulative dose of 15 mg/kg body weightIntravenous to induce Doxorubicin Cardiotoxicity.

Group V Test Group -1 Indian Cobra Envenomation 0.216 mg.IM Followed by Inj PVASVin calculated dose as 0.36 ml IV at same time 9 mg of *Suvarna gairik* with plain water orally twice daily for 7 days.*Suvarna gairik* will be given orally as cardioprotective drug and followed by Inj PVASV intravenous as antidote.

Group VI Test Group -2 Aluminium Phosphide tab 2.7 mg orally followed by 9 mg of *Suvarna gairik* with plain water orally twice daily with water for 7 days. *Suvarna Gairik* will be given as cardioprotective drug.

Group VII Test Group 3- Inj. Doxorubicin 2.5 mg /kg body weight in 6 equal injections alternatively for two weeks to make a total cumulative dose of 15 mg/kg body weight. IV to induce Doxorubicin Cardiotoxicityand 9 mg of *Suvarna gairik* with water orally twice daily from 1 st day of Doxorubicin administration for 15 days.

3. EXPECTED RESULTS

The survival Rate and survival time will be higher in Test groups. There may be statistically significant difference in cardiac biomarkers in vehicle control group and Disease control group and Test group.

4. DISCUSSION

Acute poisoning is being major problem. It is seen that in developing and developed countries poisonings cases are increasing and needs hospitalization and and its fatal outcomes are also noticeable. In India mortality rate due to poisoning varies around 20% [14]. Even if there is excess cases of poisoning and snake bite if appropriate strategies are used mortality can be reduced. Early diagnosis and prompt primary intervention is necessary. Before spread of poison or before absorption of poison immediate treatment at initial stage of poisoning or in snake bite will reduce duration of hospitalization and possibly mortality [15]. Poison induced Out hospital Cardiac arrest (P-OH-CA) may be prevented by prompt primary intervention [16]. Most of the time causative factor for poisoning is unknown and it is difficult to decide specific emergency antidote. Here it is need to increase survival time by emergency management which can be used as golden period for further confirmatory diagnostic investigations and specific management. It is needed to study the effective primary interventions which may useful to prolong life at tertiary care hospitals and may reduce mortality rate in poisoning. Proper integrated emergency management with modern and alternative medicine may increase survival time and reduce the fatality rate in acute poisoning. Agadtantra is special branch of Ayurveda related to poisoning. *Agadas* (Ayurvedic antidotes) from Agadtantra are proven beneficial for skin manifestations due to allergens [17-18]. Emergency treatment modalities mentioned for the poisoning should be evaluated on the basis of modern parameters. *Hridyavaran chikitsa* (Cardioprotection) is one of the treatments. If due to *Hridyavaran chikitsa* (cardioprotection) survival time is increased then it can be useful to give enough time to attain pharmacological action of specific antidotes. It is scientifically proven that many Ayurvedic drug have better results on cardiac diseases and also in rare diseases [19,20,21]. It is need to explore the Ayurvedic drugs safety on modern parametersand use them with modern line of treatment [22].

Gairik is natural hematite mineral. Red ocher is unhydrous iron oxide. It has cooling and antibilious activity. It prevents hemorrhage. It gives reliefs in hiccups. It can be used in eye

Table 1. Group distribution

Group Distribution	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII
	Vehicle control group (VC)	Disease control group 1 (DC-1)	Disease control group 2 (DC-2)	Disease control group 3 (DC-3)	Test group 1 (Test GR1)	Test group 2 (TestGR2)	Test group 3 (Test GR3)
No.of Rats	8	8	8	8	8	8	8
Sex of Rats	4 male 4female	4 male 4 female	4 male 4 female	4 male 4 female	4 male 4 female	4 male 4 female	4 male 4 female
Weight	200gmto250gm	200gm to 250gm	200gmto 250 gm	200 gm to 250 gm	200 gm to 250 gm	200 gm to 250 gm	200 gmto 250 gm
Intervention	Ro water orally	Indian Cobra Envenomation Followed by Inj PVASV	Aluminium Phosphide poisoning	Inj. Doxrubicin cardiotoxicity will be induced	Indian Cobra Envenomation and Followed Inj PVASV and Suvarna Gairik	Aluminium Phosphide poisoing followed by Suvarna Gairik	Doxrubicin cardiotoxicity and Suvarna Gairik
Route of administration of Drug	orally	Indian Cobra Envenomation IM and Inj PVASV IV	Aluminium Phosphide Given orally	Inj. Doxrubicin IV	Indian Cobra Envenomation IM and SuvarnaGairik with RO water will be *Given* orally then Inj PVASV IV	Aluminium Phosphide Given orally Suvarna Gairik *Given* orally with RO water	Suvarna Gairik with plain water Given orally aspre-treatment with INJ Doxrubicin IV
Drug Dose	-	Indian Cobra Envenomation 0.216 mg.IM once Followed by Inj PVASV 0.36 ml IV once.	Aluminium Phosphide tab 2.7 mg orally once with water.	Inj.Doxorubicin 2.5 mg /kg body weight in 6 equal injections alternatively for two weeks to make a total cumulative dose of 15 mg/kg body weight. IV	Indian Cobra Envenomation 0.216 mg.IM Followed by Inj PVASV in calculated dose as 0.36 ml IV at same time 9 mg of *Suvarna gairik* with RO water orally twice daily for 7 days.	Aluminium Phosphide tab 2.7 mg orally followed by 9 mg of *Suvarna gairik* with RO water orally twice daily with water for 7 days.	Inj. Doxorubicin 2.5 mg /kg body weight in 6 equal injections alternatively for two weeks to make a total cumulative dose of 15 mg/kg body weight. IV 9 mg of *Suvarna gairik* with RO water orally twice daily from 1 st day of Doxorubicin administration for 15 days.
Duration	7 days	7 days	7 days	15 days	7 days	7 days	15days

disorders, bleeding disorders, hiccups, vomiting, *visha vikara* (disorders due to poison), itching, burning sensation, fever, menorrhagia, metrorrhagia disease of abdomen. It is cheap, easily available and can be stored in clinics without much criterias hence this drug is chosen for the study. Integrated medical treatment may reduce the mortality due poisoning. The Indian cobra bite can be rapidly fatal. It may take as early as 60 minutes. It causes hypertension and increased cardiac output and it is followed by myocardial depression and asystole. In Indian cobra envenomation if cardiotoxicity occurs mortality approaches towards 100 %.

Aluminum phosphide is preferred rodenticide used for preservation of grains but one of agent commonly used for the suicide purpose. In aluminium phosphide poisoning severe cardiovascular complications such as hypotension, shock, arrhythmias, congestive heart failure, with toxic myocarditis are seen and in rare cases ST- segment elevation myocardial infarction and other ECG changes are also seen. In these cases of aluminium phosphide poisoning, cardiotoxicity should be monitored as early as possible for better outcome [23]. Few of the related studies were reviewed [24-26].

Doxorubicin cardiotoxicity may be acute; manifestations may be seen in 2-3 days of its administration.
So here the attempt is made to substantiate the cardioprotective action of *Suvarna Gairik* in poisoning due to Cobra Snake Venom, Aluminium phosphide and Doxorubicin cardiotoxicity.

5. CONCLUSION

The results will be analyzed and inferred to get final conclusion. If statistically significant results obtained then *Suvarna Gairik* (Red ochre) can be used as cardio protective drug with other cardio protective drugs mentioned in Ayurveda. It may helpful in reducing mortality rate due to poisoning. This research study will be helpful to evaluate the efficacy of emergency Hridyavaran chikitsa (cardioprotection) in poisoning on modern parameters. The present study will be helpful to researches as evidence for the cardioprotective effect of *Suvarna Gairik*. Further clinical research can be done to see the cardioprotective effect of *Suvarna gairik* in poisoning. Limitation of the study is that the subjective parameter in acute poisoning cannot be assessed in experimental study.

CONSENT

It is not applicable.

ETHICAL APPROVAL

An experimental study is designed with Animal ethics committee approval reference no. DMIMS (DU)/IAEC/2019-20-09 dated 30/09/2020.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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