

## PHARMACEUTICAL ANALYSIS OF HEART RATE VARIABILITY IN NONPOISONOUS SNAKE BITE.

Arvind Singh\*

*\*Associate Professor, Department of Pharmacy, Rameshwaram Institute of Technology and Management, Lucknow, U.P.*

**Corresponding Author:**  
[aks.jpab@gmail.com](mailto:aks.jpab@gmail.com)

### INTRODUCTION

Every year, about 5.4 million snakebites occur worldwide. These cause up to 2.7 million envenomings, almost 138,000 deaths, and 400,000 cases of sequelae or disability [1,2]. This serious public health problem is a neglected, occupational disease in subtropical and tropical countries in Asia, Africa, and Latin America [1]. Every year, two million snakebites occur in Asia, with India presenting more than 46,000 deaths each year [1,3]. In Africa, snakebites are estimated to cause 435,000 to 580,000 accidents annually, with a range of 7000 to 32,000 deaths in sub-Saharan Africa, of which 3500 to 5400 deaths occur in West Africa [1,4–7]. In Latin America, there are 137,000 to 150,000 snakebite reports and 3400 to 5000 deaths per year [8]. In developed countries in North America and Europe these numbers are much lower. In North America, 3800 to 6500 annual cases with up to 15 deaths are reported, while Europe experiences around 7500 cases and up to five deaths per year.

Snakebites are associated with poverty, and the most at-risk groups include farmers and their families, fishermen, hunters, woodcutters, indigenous people, and indigents, as well as people who do not have access to adequate health and educational systems [6,8,11]. Children and pregnant women are also considered risk groups for this neglected disease, with children often being bitten when they are playing outside, as curiosity might entice them to touch snakes. Due to the immaturity of their immune systems and low body weights compared to adults, envenomings in children are often severe. In pregnant women, snakebite envenoming has been documented to occasionally cause abortions, mainly due to hemorrhage [8,12]. In May 2019, the World Health Organization (WHO) launched a program to prevent and control snakebite incidents via (amongst other strategies) improved access to effective and safe treatment for the most affected communities, thereby aiming to reduce snakebite mortality and morbidity by 50% by 2030. In addition, the WHO encourages the search for new treatments, diagnostics, and preventative measures that can lead to faster recovery of snakebite victims or avoidance of victims being bitten in the first place

No venomous snake is large enough to consider human beings as prey, and the main reason for human snakebite envenomings is that the snake defends itself against what it considers an imposing threat. However, as venom is metabolically costly to produce [14] and may not in itself immediately deter an imposing human or predator, as most venoms need time to exert their toxic effects, snakes may benefit from delivering warning bites devoid of venom ('dry bites') to predators and threats, thereby saving their venom for future prey. Thus, in many encounters, where snakes bite human victims, the victim may fortuitously only receive a dry bite.

Cardiac events are rarely associated with ophidian accidents, especially those involving snakes of the Elapidae family. We report on a snake bite victim who, within a few hours after the accident, developed myocardial infarction in the inferior wall with good clinical evolution.

### LITERATURE REVIEW

**Morusupalli, Raghavendraro et.al. (2022)** Cold-blooded, elongated snakes are found on the land, in the sea, in lakes and deserts. Simple puncture wounds to life-threatening disease and death may result from snake bites. There are a large number of non-venomous snakes. Serious snake bites should be handled very seriously at all times. Every year, more people die from snakebites in India than any other nation. Getting bitten by a snake is a life-threatening medical emergency. More than 300 snake species may be found in India. Around 60 snake species are capable of posing a threat to people, according to this study. In many countries, snake venom is still a severe concern. A neglected medical issue, snakebite is responsible for a large number of deaths and long-term disability in tropical nations across the globe. Rapid, on-site awareness devices for snakebite are highly recognized because of their usefulness in both clinical and forensic medicine. Monovalent antivenom treatment is being advocated to target venom neutralization in envenomed individuals with the least negative effects. It is possible that a kit for detecting snake venom may lower fatality rates.

**Majumder D, et.al. (2014)** In India, snake bites are a serious yet underreported public health issue. In India, there have been just a few community-based epidemiological research on this topic. There were a lot of research based on data from

the hospital. Only 22% of snake bite victims in the state reported to a health facility. Research goals include determining the prevalence of snake bite in eight West Bengal blocks in the South 24-Paraganas district and investigating the underreporting of snake bite mortality in local health facilities throughout the study period. Sources and Procedures: A community-based epidemiological survey of 1.9 million people was used to conduct a

retrospective study of snake bite data. From January 2009 to October 2010, a door-to-door survey was conducted to compile an epidemiological profile of snake bites in the preceding two years. It was determined that snakebite fatalities were underreported by comparing direct survey data with official hospital statistics in the same location. The overall number of snake bites in the research region was 4871, according to the results of the survey. Both sets of data showed a substantial discrepancy (direct survey and official data). In the United States, just 7.23% of snake-bite fatalities were recorded. Only 22.19% of snake-bite victims went to the hospital, according to a new report. The common krait bite accounted for over 65.7% of all snake bite fatalities, with the majority occurring between June and September. To sum it up, India's official reporting system is woefully inadequate. The health authorities should pay greater attention to snake bites.

**HS Bawaskar, et.al. (2014)** Between January 2005 and August 2011, the Mahad General Hospital treated 141 people who had been poisoned by krait bites. The clinical indications and symptoms that precede the development of neuroparalysis were examined. Males comprised 56 percent of the patients. Between midnight and 5:00 a.m., 140 people were reported to have been injured. 85% of patients woke up in the night with stomach colic and 72% with chest discomfort. Vomiting (42%), sweating (17%), and excessive salivation (35%) were among the symptoms reported by patients, according to the study. On arrival at the hospital, 78% of patients exhibited dysphasia with saliva pooling, and 89% had eyelid heaviness and ptosis; 12.5% of patients died on route to the hospital, while 13.47% died during treatment. 48% of the 74.46% of those who were able to recover had to be kept alive by mechanical ventilation. Krait bite poisoning caused a person to suddenly have stomach colic and vomiting while sleeping on the floor without a mosquito net.

**singh A, et.al. (2015)** Snakebite is a common medical emergency in rural areas, where snakes are more prevalent. Many nations across the globe, particularly those in South Asia, are grappling with this serious issue of public health. Between 2010 and 2012, a tertiary care teaching hospital in rural Haryana was conducting a research on the epidemiological features of snakebite among human snakebite patients admitted to its emergency room. In addition, we wanted to look at other possible predictors of snakebite outcome. MMIMSR's emergency ward in Mullana, Haryana, treated snakebite patients between June 2010 and May 2012, collecting addresses and phone numbers for the purpose of this cross-sectional investigation. Data about the individuals' epidemiology was gathered by conducting interviews with those who were qualified for the research. Records provided the necessary clinical information. The bulk of victims, 49.4%, were between the ages of 31 and 45, followed by 32.91% of those between the ages of 16 and 30. An estimated 20.3% of those killed were illiterate. The bulk of those killed (48.1%) were agricultural workers and manual laborers. The most prevalent area of the body to be affected was the foot (62.03%). The majority of snakebite incidences (48.10 percent) happened when the victims were working in the fields. The majority of occurrences occurred during monsoon season (64.56%) and 41.77% of victims were bitten in the woods. Only 20.25% of the respondents sought medical treatment after contacting traditional healers (ozhas). In 55.69% of the instances, the time it took to get to the hospital was less than four hours. After receiving treatment, the vast majority of snakebite patients (83.54%) made a full recovery. Snakebite mortality in rural areas may be reduced if more people were educated about the dangers of snakes, people were sent to the hospital quickly if they were bitten, and anti-snake venom was readily available.

**Karakus A, et.al. (2015)** Despite the fact that snakebites are very uncommon, they may have devastating effects if left untreated. Snakebite patients will be evaluated in terms of medical follow-up, antivenom treatment and responses to antivenom in this research Retrospective reviews of emergency department patient data from January 1, 2006 to December 31, 2010 were conducted. A total of 125 people with snakebite-related injuries were included in the research. There were 54.4% males and 45.6% females in the total 125 cases. The average age was 34.87 19.29 years, with 65.2% of the patients being older than 30. The month of June had the highest number of emergency room visits for snakebite-related complaints, with 27 visits. Upon admission, all patients were found to be awake and in excellent health, although all had discomfort and swelling where the bite had occurred. There were only 25 snakebite victims out of the total number of patients who had bite injuries and ecchymosis. 66 individuals (52.8%) had bites on their upper extremities, whereas 58 (46.4%) had bites on their lower limbs. Twenty-five patients (20%) did not need antivenom, whereas 23 patients (18.4%) each received four doses. The antivenom was administered to six (4.8%) individuals nine times each. Other than anaphylaxis and compartment syndrome (n: 2, 1.6%), serum sickness (n: 1, 0.8%) was found in the remainder of patients. In all, 86 patients (68.8%) were admitted to the hospital's emergency department, while 25 (20.0%) were seen in the emergency department. There was just one patient being cared for and monitored in the ICU. The use of antivenom therapy in the treatment of all snakebite patients is deemed unnecessary. Continuous attentive monitoring, adequate prophylaxis, and regulated slow infusion delivery of drugs may help decrease antivenom responses and the number of associated cases.

**Mohapatra B, et. al. (2011)** For a long time, India was regarded to have the highest rate of snakebites in the world. As a consequence of insufficient data collected from medical facilities, estimates of the yearly death toll from snakebites range from 1,300 to 50,000 people. We used a national mortality survey to estimate snakebite death rates. Our analysis, which included 123,000 fatalities from 6,671 randomly chosen locations throughout the country between 2001 and 2003, was designed to be nationally representative. Non-medical field workers conducted all interviews with live respondents. Two of the 130 doctors that participated in the study independently coded the underlying reasons. Disputes were either arbitrated or reconciled in an anonymous manner. There were 562 fatalities (0.47% of total deaths) attributed to snakebites.

The majority of snakebite fatalities occurred in rural regions (97%), with men (59%) being bitten by male snakes (40%). The peak of snakebite mortality occurred between June and September, when the monsoon season is in full swing. According to the 99% confidence interval (99% CI), the number of snakebite fatalities in the United States is around 45,900 per year, or an annual age-standardized rate of 4.1/100,000 (99% CI 3.6–4.5), with higher rates in rural regions and Andhra Pradesh (5.4/100,000; 99% CI 4.8–6.0). (6.2). Uttar Pradesh, Andhra Pradesh, and Bihar had the most annual snakebite fatalities, each with an average of 8,700. (4,500). In contemporary India, snakebite remains an under-recognized

source of unintentional mortality. The overall number of snakebites in the world may be overestimated due to India accounting for a significant share of the worldwide total. More antivenom provision to the 13 states with the greatest snakebite frequency, as well as increased community education, might help lower the number of snakebite fatalities in India.

**R. Dehghani, (2014)** Snakebite envenomation is a life-threatening condition that must be treated as soon as it is discovered. Because of the ideal climate conditions for snakes to survive and thrive in south Iran, several snakebites are reported every year. 195 snake bite cases (Reptilia: Squamata: Viperidae; *Echis carinatus sochureki*) reported to 10 rural health clinics, two health care stations, and the Hormozgan University of Medical Sciences (HUMS) Haji-Abad Central Hospital were examined in this retrospective cross-sectional research. Using seasonal time series models, the monthly pattern of snakebite incidents was described and predicted using a linear model. Males (70%) and those from rural regions (79.5%) made up the majority of these patients. More than a third of the victims were between 20 to 29 years old (32%) while the average age of the victims was 33 (17.0). 80% of snakebites occurred outdoors, 97% occurred on hands and legs, and 61% of snakebites occurred among the jobless and farmers. Most snakebite cases (32%) occur overnight, while 51% occur during the summer. The bite areas hurt for the majority of individuals (about 70%). The sex of the patient differed significantly ( $2 = 7.764$ ,  $P = 0.021$ ) depending on whether the bite occurred inside or outside. Snakebite incidence was predicted using a mixed seasonal autoregressive moving average, ARMA (1,0) (1,1)<sub>12</sub>, which was shown to be the most accurate method. Summer is snake bite season in the area, so homeowners should take extra precautions.

**Dehghani R et.al. (2014)** As a result, little is known about the epidemiology of snake species that venomous to humans in Iran. Venomous snakebite is a common medical issue in Kashan, Iran. Regional medical clinics and staff would benefit from accurate information on snake species responsible for envenomation in this area, which could help them better treat their patients. Sources and Procedures: All patient information was gathered from Kashan and its surrounding areas for this cross-sectional study. Information about how to correctly classify snakes that can inflict injury or death was examined. Patients were also given an overview of how to get a diagnosis and treatment plan together in general terms. The taxonomic classification of snakes responsible for bites was confirmed in a laboratory using key anatomical features and morphological characteristics. Results: 46 snakes were examined in total. Of these, 37 (80%) were non-venomous species, and 9 (20%) were venomous. Viperidae comprised 78% of all poisonous snake species, while Colubrids accounted for just 22%. There were a number of viperid species found in the area, including the *Macrovipera lebetina obtusa*, *Pseudocerastes fieldi*, and *Echis carinatus*. *Malpolon monspessulanus insignis* and *Psammophis schkari* were the two colubrid species that were found in the study area. A total of five species of venomous snakes were found to be responsible for envenoming people in the Kashan city area. A new species of viper, *P. fieldi*, was discovered in central Iran for the first time.

**Bhalla G, et.al. (2014)** Snake bites are a common occupational and rural danger in India because of the country's abundance of exotic snakes. The most frequent venomous snakes in Maharashtra are the cobra, Russell's viper, saw-scaled viper, and krait. This occupational danger is often overlooked by doctors because of the high morbidity and death. To investigate the prevalence of poisonous and non-poisonous snake bites in a part of Western Maharashtra, India, with regard to age, sex, occupation, part of the body bitten, time of bite, and seasonal variation, and the types of poisonous snakes common in this area and their clinical manifestations, as well as systemic envenomation from various types of poisonous snakes and their effective management in reducing mortality rates. Procedures & Methods: A tertiary health care facility in Maharashtra did a retrospective analysis between May 2010 and May 2012. A total of 150 individuals were evaluated in our facility. The study's 150 participants experienced 76 incidents of dangerous snake bite and 74 cases of non-poisonous snake bite. There were 42 viperine snake bites, 21 neuromuscular bites, and 13 locally toxic (LT) snake bites among the 76 dangerous snake bites. Snake bites are a frequent and potentially fatal emergency in the research region. Prognosis and death rates for patients who are admitted to the hospital later when they have consumptive coagulopathy, renal failure, or respiratory failure are all worse. Pulmonary embolism, intracranial hemorrhage, and dispersed intravascular coagulation were all detected in this investigation (DIC).

**Hsiang AY et.al. (2015)** Debate has long raged over the evolutionary and ecological origin of snakes, both the overall snake group (Pan-Serpentes) and the crown snakes (Serpentes) (Serpentes). Preliminary research into snake evolution has been hindered by a lack of good paleontological material on early stem serpents, which has contributed to the lack of a comprehensive study of serpent beginnings. There has never before been a complete analysis based on numerous ancestral state reconstruction methodologies of ancestor of crown snakes and the ancestor of the snake total-group ancestor. Using fresh data from the fossil record, new anatomical data on the three stem snakes *Najash rionegrina*, *Dinilysia patagonica*, and *Conopsis precedens*, and a better grasp of the distribution of phenotypic apomorphies across the main fossil and recent snake clades, we use a combined-data method. In addition, we use both innovative 'tip-dating' and standard node-based methodologies to infer time-calibrated phylogenies, revealing fresh insights into snakes' early evolutionary history. In-depth ancestral state reconstructions show that both the crown snake and the total-group snake's progenitor were nocturnal, broadly foraging, non-constricting stealth hunters in their ancestral state reconstructions. Prey that was less than the size

of their heads is presumably that the snake and the lizard in water were not able to breathe and therefore they had to come out of the water. This node suggests that the snake total-group evolved on land around the middle of the Early Cretaceous (approximately 128.5 Ma), with the crown-group following about 20 million years later, during the Albian stage. An abundance of henophidian snake variety emerged after the K-Pg (Cretaceous-Paleogene) mass extinction, and our predicted divergent dates gave good support for this. Our findings show that the snake total-group may have formed on Laurasia, despite the fact that the snake crown-group most likely started on Gondwana. Our research sheds light on the origins of snakes, including when, where, and how they first appeared. It also paints the most comprehensive picture yet of snakes' early evolutionary history. It's important to use fossils and phenotypic data in integrated studies for both inferences of topology and reconstruction of ancestral states.

**Kaul S et.al. (2021)** Rapid, on-site identification of snakebite is much sought after because of its clinical and forensic relevance in medicine. As a result of its weak venom neutralization capabilities and diagnostic repercussions exhibited as adverse immunological responses, polyvalent antivenom treatment is limited in its use in situations of such envenomation. An antibody (AB1; IgG1– chain; Kd: 31nM) produced against recombinant cytotoxin-7 (rCTX-7; 7.7kDa) protein of the elapid venom has been created for accurate molecular identification of venoms from the big four snakes (elapids). *Naja naja* and *Bungarus caeruleus* were the only two poisonous snakes to be specifically recognized by the monoclonal antibody, whereas the viperidae species among the big four venomous snakes were not. For the detection of *N. naja* and *B. caeruleus* venoms, the kit achieved limit of quantitation values of 170 pg/L and 2.1 ng/L in spiked buffer samples and 28.7 ng/L and 110 ng/L in spiked serum samples, respectively. In accordance with current medical criteria, this kit has significant potential for identifying elapid venom from the major four snakes for efficient prediction of an envenomation.

**Fuchs J, et.al. (2019)** The Beautiful Pit Viper *Trimeresurus venustus* (or *Cryptelytrops venustus*), a green pit viper endemic to Thailand and Malaysia, is the subject of this case study. Adult *T. venustus* bit an otherwise healthy snake breeder's third finger when it was being removed from its feeding box, which had no prior medical history. Within an hour of the bite, his hand had swelled to the size of a fist. It took 26 hours after the bite for him to be released from the hospital after just receiving symptomatic treatment with antibiotics and painkillers. He never developed any hematological abnormalities like coagulopathy or bleeding. Another instance presented as a conference presentation had the same clinical course as our patient, which was confirmed by two more cases that were reported to our Poisons Centre. All patients healed without the need for antivenom after just receiving symptomatic treatment. Bites from *T. venustus*, on the other hand, seem to cause fewer and milder symptoms.

**Kumara, R. (2016)** In tropical and subtropical countries, snakebite is the most prevalent health concern. Snakebite is one of the leading causes of death in underdeveloped nations, particularly among farmers. In the WHO's list of neglected tropical illnesses, snakebite is included. Violent poison enters the bloodstream immediately after the bite and attacks several organs. When an animal bites you, the venom works on your Autonomic nervous system, causing your heart rate to slow down. In addition, the venom directly affects the cardiac muscle, reducing the heart rate by decreasing the force of contraction. Non-invasive electrocardiographic indicators, such as heart rate variability (HRV), may be used to detect changes in HRV in snakebite patients. An increase in HRV (P-Value 0.05) after a snake bite envenomation is regarded statistically significant. We came to the conclusion that the acute effect of snake envenomation affected the autonomic regulation of the heart rate as indicated by heart rate variability. Treating snakebites with antivenom led to a shift in balance from parasympathetic to sympathetic dominance.

**Gutiérrez, J., et. al. (2017)** It is estimated that snakebite envenoming kills more than 100,000 people and injures more than 400,000 people every year. Snakebite envenoming reinforces the cycle of poverty in the rural tropics, where the poorest people are most at risk. All of the toxins found in snake venom are composed of complicated protein combinations. The wide range of clinical symptoms in envenomings, from local tissue injury to potentially life-threatening systemic consequences, may be attributed to the wide variety in snake venom composition. Only intravenous antivenom injection can effectively combat envenoming. Antibiotics and analgesics are also often utilized in the treatment of patients. New toxin inhibitors and recombinant antibody technologies are being investigated as potential treatment solutions. The World Health Organization (WHO), the research community, antivenom manufacturers, regulatory agencies, national and regional health authorities, professional health organizations, international funding agencies, advocacy groups, and civil society institutions must work together to combat snakebite envenoming on a global scale.

## OBJECTIVE

1. To analyze variation in heart rate.
2. To evaluate clinical manifestations of non-poisonous snake bite and its management
3. To evaluate the effect on cardiac profile in patients with snake envenomation and its complications

## RESEARCH METHODOLOGY

### Sample Collection

A total of 586 patients with suspected snake bites admitted to Pariyaram Medical College, Kannur, Kerala during study period.

### Assesment for evidence of envenomation

All the patients will be assessed on four lines i.e. for evidence of haemotoxicity, neurotoxicity, cardiotoxicity and local toxicity. All assessment will be done repeatedly for at least 24 hours, detailed one at presentation and simple ones at two hourly intervals, after a suspected bite before declaring a non–venomous snake bite.



## Haemotoxicity

It manifests as spontaneous continued oozing of blood from site of bite or site of intravenous access, echymosis on surface especially on pressure points and bleeding from mucous membranes like conjunctival echymosis, epistaxis, haemoptysis, haematemesis and haematuria. If nothing so was visible at the time of first examination then "Twenty-minute whole blood clotting test" will be performed by drawing 5 ml of blood in disposable plastic syringe, left undisturbed for 20 minutes, and observed for evidence of clot formation. If clot doesn't form then envenomation has occurred. If frank evidence of haemotoxicity is evident then the evaluation will be extended to assess for possible intracranial hemorrhage,

intraperitoneal hemorrhage, gastrointestinal hemorrhage, excessive menstrual loss and intramuscular haemorrhage, which may present as compartment syndrome i.e. compressing some nerve or blood vessel. Effects of volume depletion and massive release of hemoglobin may lead to acute renal shutdown. Measurement of hourly urine output and testing of urine for haemoglobin will be started to make necessary adjustments in fluid and electrolyte management i.e. fluid overload and hyperkalemia.

## Cardiotoxicity

It will be assessed by routine parameters i.e. heart beat, blood pressure (BP), postural hypotension, dysrhythmias and electrocardiogram (ECG) monitoring. Assessment is difficult as fear, panic, dehydration, intravascular volume loss and hypovolaemia due to hemorrhage from haemotoxicity, all will influence the cardiovascular system (CVS). These factors will be kept in mind when analyzing the haemodynamic status. Cardiotoxicity will present as tachycardia, dysrhythmias, hypotension and myocarditis with relevant changes in E.C.G. Cardiotoxicity alone is rare. It is usually in company with hemotoxicity and local necrosis.

## Management

After documenting the evidence of envenomation, anti-snake venom (ASV) administration will be started rapidly. Depending upon the clinical judgment of severity, one to four vials of anti-snake venom (10 ml each) diluted in isotonic saline to make 10 ml volume will be given intravenously over 60 minutes while watching for signs and symptoms of anaphylaxis like skin rash, bronchospasm, urticaria, tachycardia and hypotension. At the end of one infusion, patient will be re-assessed. If evidence of envenomation is still present, another dose of four vials was repeated again with same precautions for anaphylaxis. End point of treatment will be considered to be the clinical neutralization of venom evident by arrest of further progression of muscular weakness, restoration of coagulability of blood, arrest of further progression of local swelling and stabilization of cardiovascular status.

## EXPECTED OUTCOME

Overall analysis of results suggests that, cardiac involvement is uncommon in snake envenomation. As occurrence of sinus tachycardia in snake envenomation will be most likely due to non-cardiac causes. Mortality results suggest that, cardiovascular involvement may not be responsible for mortality in snake envenomation. 80% of snakes in our area are non-poisonous, 2. Evidence of envenomation is the only indication of ASV administration, 3. All the evidence of envenomation must be neutralized by adequate dose of ASV, 4. Even delayed administration of ASV is effective in neutralization of the venom.

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