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FOCUS ON THE VARIOUS CORRIDORS OF SNAKE BITE ENVENOMATION TREATMENT- A REVIEW

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ABSTRACT

Snake bite is an important and serious global health issue. Till date anti snake venom serum is the only therapeutic remedy available for treating the snake bite victims. Infusion of ASV may lead to adverse reactions ranging from pruritus, urticaria to potentially fatal anaphylaxis. The development of ASV is also a costly and time consuming process requiring ideal storage conditions. Though Anti Snake Venom Serum (ASV) is the only remedy available to treat snake bite victims successfully till date, considering all above difficulties research workers all over the world are constantly in search of a cheap and readily available easy formulate remedy for treating snake bite victims. A few chemical constituents of the plants have been so far identified for their anti snake venom effect. Traditional remedies from plants used in the treatment of snakebite victims have a number of potential advantages over the ASVs. Considering these limited number of published reports, one can say that many such plants which can provide potent immunization against snake bite poisoning are yet to be evaluated systematically. Research is also being carried nowadays to produce the immunity against the specific snake venom by using a targeted drug delivery system. Much emphasis is also given on the correct detection of types of venoms injected in the body of the victim and successful rehabilitation of patients after treatment. One can say that a permanent and suitable protection against any snake bite poisoning will be fulfilled in the near future and liposomes may become the way for developing a new and effective anti snake venom dosage form. In the present paper some of the aspects of snake bite treatment from ASVs to the recently developed measures of detecting snake bite envenomation and therapies have been discussed.

Key words: Snake bite envenomation, Remedies, Medicinal plants, Liposomes.

INTRODUCTION

Historical Development of Traditional Treatments for Snakebite Poisoning in India

Though anti snake venom serum is the only therapeutic remedy available for treating the victims till date, much scientific attention has also been given to the identification and isolation of plant derived principles for the treatment of snakebite victims during last two decades. As such use of the medicinal plants for the treatment of snakebite poisoning is a common and age-old practice. Many plants are reported to inactivate snake venoms. Search for the exact antidotal combination for treating snakebite victims goes very far behind in the history of Indian Medical Services (Mhaskar *et al.,* 1931). In 1908 at the request of the Director General, Indian Medical Service, efficiency of a remedy called "Surucuina" was experimentally tested against the all kinds of poisonous snakes at Pharmacological Laboratory, Haffkine institute, Bombay. This remedy was reported to have gained some reputation as an antidote. In 1909 under the orders from the Sanitary Commissioner with the Government of India another Mexican remedy called "Ofidina" was tested experimentally for the same purpose by the same workers. During the same year a specific antidote remedy was submitted by a Hakim of United Provinces, who was of belief that his ancestral remedy was effective against all kinds of poisonous snake bites. Another antidotal combination named "Viborina" was also experimentally tested in 1910. It was said to have acquired considerable fame in Venezuela for treating poisonous snake bites. In 1912 the then Civil Surgeon of Hugli had submitted an unknown plant for experimental trial.

Subsequently in 1914 the Acting Consul for France in Bombay, forwarded an ointment made by some Mr. M. Robert of Bordeaux, who had claimed of curing more than 2000 victims of snake bite with the same and he was anxious of testing his remedy in India. In another incident, at the request of Sir Leonard Rogers I.M. S. who was also the manager of Sutna Stone and Lime Company sent some roots and sticks of the shrub called "Goor Boinchee" (Bengali) for the trial in 1915. The remedy was said to have cured two cobra bite patients at that time. During the same year another combination named "Antitoxicum" was submitted by one Mr. E. D. Fransz with his directions and copies of testimonials claiming the remedy as an "Infallible" cure for poisonous snake bite. "Tiriyaq" an antidote against the poisonous snake bite was sent to the Haffkine Institute Bombay, in 1916 by the then Inspector General of Civil Hospitals, Central Provinces

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for the experimental trial. Which was carried out using dogs as a model against Cobra, Krait, and Russell's viper and *Echis carinatus* bite subsequently showing its uselessness. Same remedy was again submitted in 1929 for the evaluation by some workers asking omission of dogs from the experimental trials as the drug was not supposed to be active in dogs against snake bites. In 1920 a "pod" of white champa was forwarded by a Senior Grade Sub Assistant Surgeon, Deccan College Dispensary, Poona for the evaluation. During the same year a "root" was sent by the then Her Highness, The Ruler of Bhopal for the experimental trial against all kinds of poisonous snake bites. On 14th February 1921 at the request of the then Director General of Industries and Commerce Secretariat, H.E.H. the Nizam's Government, Hyderabad Deccan, Mr. Sayed Mehdi Hassan brought his remedy to Haffkine Institute, Bombay for the experimental trial and evaluation against poisonous snake bite.

The remedy was named "Payam-i-Hayat" and was claimed to be found effective against cobra and daboia bite in two dogs. This experimental evaluation of different druy combinations and remedies claimed to be effective in treating poisonous snake bite victims continued consistently for some more years, till the development of Anti snake venom serum (ASV). Further in 1923, a Mexican antidote called "El Elixir Antiviperino" was forwarded by the then Director General, Indian Medical Service. It was believed that the the mixture was effective in curing snake bite victims, rabbies and varicose veins. At the same time British Leagation, Mexico submitted another antidotal combination "Lexin" for the trial with its complete method of preparation.

It was claimed that the remedy was successfully tried by the maker himself before submission. In the same year, another "infallible cure" was sent for the trial to Civil Surgeon and Sanitary Officer Gulbarga by the Chemical Examiner to the Government of Burma, Rangoon. Further in June 1928 Firozuddin from Jammu was reported to came all the way from his native place to give demonstrations of his "cure" against poisonous snake bite either on himself or a dog. He was introduced by the then Superintendent of Jamsetji Jeejeebhoy Hospital, Bombay. In 1929 the International Trading Company, Bombay submitted a sample of "lobelin" prepared by M/s C. H. Boehringer Sohn. Hamburg, for experimental evaluation of its anti snake venom efficacy, claiming that lobelin is advantageous in snake bite poisoning.
Apart from all these antidotal combinations, total 328 medicinal plants and 184 different combinations are reported to have anti snake venom activity in Ayurvedic and Classical literature, since ancient times viz. Charak Samhita, Nighantu, Sushruta Samhita, Ashtanga Hridaya, Sharangdhar Samhita, Raschintamani, Rasratnakar, Bhavprakash, Ayurved prakash and Yogratnakar etc. Unfortunately all of these above stated remedies, medicinal plants and Ayurvedic preparations are reported to have no anti snake venom property by the same workers in their exhaustive study (Mhaskar *et al.,* 1931).

Traditional Herbal Medicines and Pharmacological Evaluation of Crude Drugs for Their Anti Venom Effect

It has been observed that in rural and remote areas as well as in hilly regions incidence of snakebite is quite frequent and due to the lack of ample medical facilities and rare availability of the anti snake venom serum in the rural hospitals, majority of the patients die before reaching the hospitals and many more cases go unreported as well. Tribal people of these areas mostly treat the snakebite victims by local herbs and medicinal plants. Largest number of snakebite fatalities is reported each year in these areas. Commonest species of venomous snakes found in these regions are from elapidae family viz. cobras and kraits. Poisoning cases are always frequent in rainy and summer season in the villages. Villagers and farmers also suffer from the attacks of highly poisonous kraits during night. Viper bites are also reported in bushy and thick areas of the forests. Though adivasis of these regions are not aware of the presence of any active ingredients and their exact biochemical reactions against enzymes of snake venoms, scientific reports about useful actions of these medicinal plants are always found and descriptions of these plants are also available in classical literature.

Tribals of such regions treat affected persons by local herbs. Snake charmers and witch doctors are the first line defense against the acute emergency of snake envenomation. These traditional healers treat snakebite victims by administering decoctions, infusions or fresh juice of the aerial parts of the herbs. Sometimes fresh pulp of the leaves or whole plant is applied to the bitten part. Use of the decoctions of *Dichrostachys cinerea* W and A, locally known as "Hiver" (Leguminosae), and some other plants for this purpose has already been reported (Bhamare PB 1955). On the similar grounds active ingredients of the medicinal plants are assayed for their anti snake venom activity by using different scientific methods.

Current Status of the Snake bite Treatment in India

Snake bite is a well known occupational hazard for farmers, fieldsmen and outdoor workers. Snakebites are a major problem in rural parts of India. Approximately 50000 deaths are reported annually due to snakebite poisoning. As such five important clinical syndromes of snakebite envenomation are stated:

- Local envenoming (Swelling of bitten area etc) with bleeding or clotting disturbances especially with Viperid envenomations.
- Local envenoming (Swelling etc.) with bleeding and clotting disturbances, shock, kidney injury and neuroparalysis.
- Local envenoming (Swelling etc.) with paralysis.
- Paralysis with minimal or no local envenoming.
- Paralysis with dark brown urine and acute kidney injury.

Currently Proposed and Utilized Treatment for Snakebite Envenomation

Viperid Envenomation

Anti snake venom serum (Optimum dosage)
Adrenaline, first aid and rapid transport to hospital
Corticosteroids in case of anaphylaxis.
Antibiotics to treat cellulitis and various Gram positive and Gram negative infections.
Dialysis in case of renal failure.
Blood transfusion/ Blood component transfusion in case of coagulopathy.
Incisions. (If only needed)

Elapid Envenomation

- Anti snake venom serum. (Optimum dosage)
- Rapid transport, first aid and pressure immobilization.
- Mechanical ventilation to arrest respiratory failure.
- Antibiotics to treat cellulitis.
- Incisions (If only needed)
- Apart from all these standard measures, antihistaminic drugs, routine transfusion therapy, neostigmine.

Case Study Designs proposed and implemented currently

- Important health outcomes considered:
- Mortality
- Ventilator support
- Time for normalization of hematological and neurological parameters
- Duration of stay of the patient in hospital
- Need for and duration of ventilation
- Need for check on blood clotting factors
- Need for dialysis and other complications.

Parameters of Morbidity and Mortality

- Time since snake bite to administration of ASV
- Pre hospital care
- Type of care
- Antidote/ Intervention used
- Standard of care in ICU

Recommended First aid Measures (Blackman *et al.*, 1992)

Recommended first aid measures for snakebite change with the times but generally are directed towards removing venom and preventing the spread of the venom systemically. Controversies center primarily on the implementation of these measures. However following measures are followed always.

- Moving the victim out of the snake's territory.
- Placing the victim at rest.
- Reassuring the patient with cleansing the wounds.
- Generally attempts are made to identify the snake locally; sometimes killed snakes are carried to the physicians with the victim, which is not always a foolproof method.
- Immobilization of the affected part in a functional position.
- Transportation to the nearest health center or hospital.

Use of the tourniquets has long been promoted to prevent the spread of the venom through the systemic circulation. Many workers oppose this idea of using tourniquets because venom uptake occurs through the lymphatics while tourniquets occlude the arterial and venous flow which leads to the lymphedema, ischemia, necrosis, gangrene, arteriovenous fistula formation and peripheral neuritis. It is also suggested that release of tourniquet can lead to the rapid distribution of the venom causing shock and hypotension.

Administration of Anti Snake Venom Serum

While attending the snake bite victims physicians always confront the issue of correct assessment of the degree of systemic envenomation and decision on optimum dose of Anti snake venom serum to be administered.

Presently available polyvalent anti snake venom serum (ASV) is effective against all fatal four species of snakes found in India viz, Cobra, krait, Russell's viper and Saw scaled viper. Delivery of continuous administration of ASV by intravenous infusion is the best way to titrate the exact dose of ASV and it is presently practiced method of administering ASV. Rational use of Anti snake venom serum (ASV) by a specific regimen has been suggested by some workers after examining different regimens of ASV administration (Srimannarayana *et al.,* 2004).

Present tests for detection of snake venom and their clinical applications (Minton SA, 1999)

a) Enzyme Linked Immunoassay (ELISA)

It is a versatile and relatively simple method of detecting very small quantities of antigen and antibody. Reagents are inexpensive, stable and less time is required to perform the test. This technique was first adopted by British workers by using double antibody sandwich technique. This involves coating the wells of polystyrene plate with rabbit antibodies against snake venoms with some wells coated with normal rabbit immunoglobulin as controls. Coated plates can be stored in a refrigerator for at least a year. Samples of serum, urine wound exudates or tissue extracts suspected of containing venom are added to the wells and incubated. Wells then are washed and enzyme conjugates antibody added. Following a second incubation and wash, a substrate that reacts with the enzyme conjugated to the antibody yield a colour reaction is added. The ensuing reaction is read visibly or spectrophotometrically. Horse-radish peroxidase is the enzyme most widely used in the snake venom ELISA. A widely used substrate is hydrogenperoxide + o-phenylene diamine dihydrochloride. Venoms of the all medically important snakes of the respective area can be included in this detection system. Unfortunately these tests are not available for the diagnosis in rural and most of the urban hospitals.

b) Laboratory Investigations (Ray *et al.*, 2011)

Different lab tests include complete blood counts, electrolytes, glucose, creatinine, serum, amylase, creatinine phosphokinase (CPK), prothrombin time, partial thromboplastin time (PTT), fibrinogen-fibrin degradation products (FDP's), Urine examination for haematurea, proteinurea, haemoglobinurea and myoglobinurea.

c) Arterial Blood Gases and PH

For the evidence of respiratory failure in neurotoxic envenoming and respiratory or metabolic acidosis. Arterial blood gases and urine examination is repeated frequently.

d) 20 Minute Whole Blood Clotting Test (20 WBCT):

It is very useful and reliable bed side test which requires very little skill. Fresh few ml of collected venous blood is taken in a small vessel and kept undisturbed for 20 min at ambient temperature. The vessel is tipped once to see whether the blood is in liquid form or clotted. Unclotted blood indicates "hyponogenemia" as aresult of venom induced consumption coagulopathy.

e) Other Useful Test for Patient Assessment (Jobin *et al.*, 2012)

Oxygen saturation, blood pressure/postural blood pressure (PBP), CT, platelet count etc is done to assess the condition of snakebite victim in case of viper bites.

Advances in the Discovery and Development of Plant Derived Principles as Anti Snake Venom Agents

Use of the medicinal plants for the treatment of snakebite poisoning is common and age old practice. Many plants are reported to inactivate the snake venom. Though Anti Snake Venom Serum (ASV) is the only remedy available to treat snake bite victims successfully till date, research workers all over the world have observed some antidotal properties of different medicinal plants *in vivo* or *in vitro*. A few chemical constituents of the plants have been so far identified for their anti snake venom effects. Majority of these plant derived constituents are either alkaloids, flavonoids or poly phenolic compounds which act by either snake venom enzyme inhibition , competitive inhibition for the the binding site of the venom or by oxidation and chemical modification of some of the major components like disulphide bridges, methionine residues of snake venoms etc.

Aristolochic acid

An alkaloid obtained from the plant Aristolochia radix (Aristolochiaceae). Chemically it is 8- methoxy-6-nitrophenanthro [3, 4 d] 1, 3 dioxole-5- carboxylic acid. Reports are available about its inhibition of direct and indirect hemolytic and edema inducing activity of Habu snake venom. (*Trimeresurus flavoviridis*). (Vishwanath *et al.,* 1987)

Gymnemic acid and its potassium salt

Successful inhibition of the enzyme ATPase, a toxic principle from Indian cobra venom by Potassium gymnemate has been reported. (Kini *et al.,* 1982)

Schummaniofocide

A chromone alkaloidal glycoside obtained from the stem bark of *Schummaniophyton magnificum* (Rubiaceae) has been reported to inactivate lethal effects of Black cobra (*Naja* melanoleuca) venom. (Akunyili *et al.,* 1986)

Ehretianone

Anti snake venom activity of this quinoid xanthene against Saw scale viper venom (*Echis carinatus*) has been explained by some workers. (Selvanayagam *et al.,* 1996)It is obtained from *Ehretia buxifolia* (Boraginaceae).

2-Hydroxy-4-methoxy benzoic acid

Reports are available about its anti venom activity against Russell's viper (*Vipera russellii*) venom. (Alam *et al.,* 1998), (Alam *et al.,* 1998), (Alam *et al* 1998)

Wedelolactone

A coumestan derivative extracted from the plant *Eclipta prostrata* (Asteraceae) is reported to have antimyotoxic and atihemorrhagic effect against South American rattle snake venom. (Mors *et al.,* 1989)

Coumarins, Caffeic acid derivatives, flavonoids, lignoflavonoids and saponins

Snake venom inhibitory activity of these bioactive principles has also been reported. Girish et al have demonstrated dose dependent inhibition of snake venom enzyme hyluronidase by different flavonoids and certain anti oxidant compounds (Girish *et al.,* 2005). As such much work is needed in this regard as exact chemical nature and mechanism of action of such plant constituents is not completely known. Secondly due to the difficulty in systemic administration of these bioactive principles at the time of snakebite, anti snake venom serum (ASV) remains the only remedy available worldwide.

Future Prospects in Development of Snakebite

Envenomation Treatment

Though anti snake venom serum is the only therapeutic remedy available for treating the victims till date, much scientific attention has also been given to the identification and isolation of plant derived principles for the treatment of snakebite victims during last two decades. As such use of the medicinal plants for the treatment of snakebite poisoning is a common and age-old practice and many examples could be sited of plants whose use can be traced to ancient times. Considering the huge amount of work done by the research workers during last two decades in this regard clearly shows that chances of treating snake bite snake bite victims chemotherapeutically will not be too far. Still much work and systematic efforts are needed to find out the exact mechanism of action of different plant derived principles in nullifying the snake venom toxicity. Most of the times it is observed that isolated active ingredients of different plant species fail to show to positive results alone in separated forms. This leads to the much needed insight into the mechanisms of secondary products of plant metabolism. Mors has described the future prospects in development of plant derived anti snake venom remedies in detail. (Mors, 1991)

By Blocking the Sites of Receptor Binding

Search for plant derived principles which are able to block the binding sites of the different receptors in human body will be emphasized in the future. Some of these compounds can inhibit the toxic effects of snake venoms by simply binding with the receptor sites, Emphasis will be on the development of agents which can block the receptor sites of snake venom without destroying its capacity to elicit the generation of antibodies. Production of such naturally derived anti sera (ASVs) will be more rewarding with lesser side effects and suffering to the animals as well as snake bite victims.

Database of Anti Venom Medicinal Plants (Amui *et al.*, 2011)

Development of Web systems that allow storage and intelligent organization of content is an important tool to help search. Medicinal plants have been used for many years to treat a great variety of diseases including envenomations by animal bites. Amui has demonstrated the development of such computational web system about medicinal plants which have anti snake venom properties.

This system consists of database of such plant, including scientific publications on this subject and amino acid sequences of active principles from venomous animals. Medicinal plants play key roles in the world health and they are the rich sources of many natural inhibitors and pharmacologically active compounds. Many of these substances structurally resemble biological compounds and this similarity is the basis of their physiological action. Pharmacological studies have revealed that the extracts and fractions of some of these plants used in traditional medicine are able to antagonize the activity of various crude venoms and purified toxins. Medicinal plant extracts have been shown to antagonize the activity of some venoms and toxins. Several plant species are popularly known as anti snake venom and have been scientifically investigated.

Many active ingredients from snake venoms have also been purified. Their molecular structures have been identified and characterized in the most advanced laboratories. Naturally in such cases, web systems have contributed immensely to scientific area with computational tools and specific systems for data analysis providing fast and reliable results and search systems. Storing data from medicinal plants with anti venom properties and venomous animals in Web system allows the relationship of these data through different search schemes, providing a helpful tool for researchers in this field. The creation of database is the solution for organizing this information and to provide knowledge of the subject, effectively assisting in the research in this area. Such Web base Plant anti venom system is available on the internet at http://gbi.fmrp.usp.br/plantiantivenom.Plantantivenom.
interface is simple contributing to a fast and functional access to the system and the integration of different data registered on it.

Fighting Snakebite Envenomation on Molecular Basis

It has been shown that many chemical constituents derived from different plant species worldwide are found to be active against the toxic effects of snake venoms (Mors *et al.,* 2000) Many different chemical moieties are found to be capable of interacting with macromolecular targets of snake venom. Snake venoms are the rich sources of proteins, enzymes and peptides which generate severe toxic manifestations in human body. Hence the mechanisms of action of medicinal plant ingredients are mainly attributed to the blocking of receptors or structures prone to the chemical attacks. Other vulnerable sites are metal ions present in different snake venoms eg. Zinc present in metallo protienases, where complex formation or chelation plays important role in inhibition of snake venom enzymes and nullification of toxicity. Considering this, one can say that plants recorded as anti snake venom in popular use have such active compounds which neutralize the toxicity of snake venoms. Hence it has become important to study the mechanism of action of medicinal plant ingredients on molecular basis to find out exact way of neutralizing snake venom toxicity.

Molecular Docking Studies and Anti Snake Venom Metalloproteinase Activity (Pithayanukul *et al.*, 2009)

Snake bite enevenomations always develop severe local tissue necrosis in snake bite victims. Venom metalloproteinases are thought to be key toxins responsible for this. Pithayanukul *et al* have reported the prominent anti snake venom activity of seed kernel extract of "Mango" *Mangifra indica* (Anacrdiaceae) and potent dose dependent inhibitory affects on caseinolytic fibrinogenolytic activities of Malayan pit viper and Thai cobra venoms *in vitro* by a major phenolic principle pentagalloylglucopyranose obtained from Mango. Molecular docking studies have revealed that the binding orientations of the phenollic principles were in the binding pockets of snake venom metalloproteinases (SVMPs). Phenollic principles have reported to form hydrogen bonds with three histidine residues in the conserved Zinc-binding motif and could chelate Zn+ atom the SVMPs, which subsequently results in inhibition of the venom enzymatic activity thereby inhibiting tissue necrosis and destruction.

Possible Immunization Against Snake Venom with Plant Derived Principles: A New Aspect of Treatment

After tentative diagnosis of the snake bite and about the type of the venom induced, first aid and supportive measures are taken up. Next, specific anti snake venom serum (ASV) is administered through the slow injection or drip. Precautions are taken to avoid adverse and allergic reactions, as some individuals are allergic to horse serum. Antivenin administered to the snake bite victim counteracts the fatal effects of the venom enzymes in the systemic circulation. All antivenins contain antibodies produced by repeated administration of small specified doses of the snake venom to the horses. These antibodies are pooled out and when administered to the bite victim produce the immunity to the patient and prevent the toxic effects of the venom. Same principle can be applied to produce the immunity against specific snake venom by using different plant derived principles.

It has been reported that seeds of a *Mucuna pruriens* are locally prescribed in Nigeria as an oral antidote to the snake bite envenomation and it is claimed that consumption of just two seeds provide immunity for an year. It has been observed that a purified fraction of protein called "gpMucB" obtained from aqueous extract of the seeds of the plant Mucuna pruriens prominently provides the immunity against the snake venoms by its Kunitz type trypsin inhibitor action in the humans. This protein fraction is thermostable both at neutral and acidic pH and because of its belonging to the Kunitz type trypsin inhibitor family; its direct anti snake venom activity is explained (Scire *et al.,* 2011). Aguiyi et al have demonstrated the immunization against cobra venom using *Mucuna pruriens* derived serum immunoglobulins in mouse models.

The neutralizing ability of the circulating antibodies was said to be assessed by challenging the immunized rats with a minimum lethal dose of purified venom after 4, 24, 72 and 186 hours. The single injection of antibody preparation produced a high and sustained immune response with high survival rates of treated animals. (Aguiyi *et al.,* 1999) It is also reported that rats pretreated with anti *Mucuna pruriens* antibodies produced by administration of seed extract of the plant conferred effective protection against lethality of *Naja sputarix* venom and moderate protection against *Calloselasma rhodostoma* venom. Same workers have explained the cross reactions between anti MPE IgG and venoms from different genera of poisonous snakes, suggesting the involvement of immunological neutralization in protective effect of MPE- pre

treatment against snake venom poisoning. In vitro neutralization experiments have reported to neutralize Asiatic cobra (*Naja*) venoms (Tan *et al.,* 2009). Considering these limited number of published reports, one can say that many such plants which can provide potent immunization against snake bite poisoning are yet to be evaluated systematically. Polypeptide nature of snake venom toxins and enzymes obviously provide vast number of targets for this purpose. In many cases, active sites have already been identified. In some instances interaction of active substances with certain enzymes of snake venoms have also been demonstrated in vitro by some workers. Still much work is remaining to be done in order to untangle the many possibilities of functional inhibition in this area.

Targeted Drug Delivery Systems and Snake Bite Poisoning: A Novel Approach (Mishal *et al.*, 2005)

Snake bite poisoning is always an acute emergency for the victim as well as for the physician. Most of the times, death ensues if patient fails to reach the hospital or if proper treatment is not available. In India, snake bite poisoning remains a serious concern for the farmers, villagers as well as field workers. This largely depends on the type of the snakes involved in biting. Mortality rate in case of elapid poisoning (cobra and krait) is always higher than viperid poisoning. (Russell's viper and Saw scaled viper). It is also interesting to note that, the quantity of venom needed to kill a70 kg healthy person is very minute. Further the time required by the venom to reach the heart is very short (hardly 6 seconds) after the bite. It is observed that all antivenins contain antibodies produced by the repeated administration of small dose of specific snake venoms to the horses.

Which when injected to the snakebite victims produce immunity against the venom. Same principle is nowadays used to produce the immunity against the specific snake venom by using a targeted drug delivery system. Laing and Theakston have demonstrated significant increased venom antibody response and protective ability of the circulating *Echis ocellatus* venom in mice with liposome, either subcutaneously or intravenously (Theakston *et al.,* 1993). A classic secondary immune response is reported by the same workers with administration of venom liposome orally or with a specific mucosal adjuvant aviridine. On the other hand rapid, sustained and protective immune response using the venom of tropical rattlesnake (*Crotalus durissus*) as a weak antigen and by administering it as a stabilized sphingomyelin cholesterol liposomes subcutaneously. (Theakston *et al.,* 1989).

This protective immune response and antibody production reported to be evaluated by the same workers using ELISA method. In another case fifty percent positive protection and immunization in mice is reported by Carvalho *et al* by subcutaneous administration of the *Bothrops jararaca* venom liposome (Carvalho *et al.,* 2000). New has described the method of producing a high and permanent antibody response by a single administration of Nigerian *Echis carinatus* (Carpet viper) venom incorporated in sphingomyelin cholesterol liposome, by subcutaneous, intravenous and by oral route. The same workers have also reported the immune response to be powerful, sustained, and lasting for a life time of a mouse. (Theakston *et al.,* 1985)On the other hand same protective response with the same venom is demonstrated by Theakston after stabilizing the venom with osmium tetroxide in the sphingomyelin cholesterol liposome (Theakston *et al.,* 1985)

Conclusion

Snake bite poisoning is a common acute medical emergency faced by the tribal and rural populations of the tropics. Unfortunately, conventional antivenoms are not only expensive, but do not effectively neutralize snake venom induced necrotic, hemorrhagic, nephrotoxic manifestations. Sometimes anti venom causes allergic reactions in patients. Mostly treatment of snake bite is normally continued till the clinical signs of envenomation disappear. The prolonged regime of injections imposes a lot of stress on the victims. Plants have reportedly been used locally to treat diverse cases of snake bites but many of the studies lack systematic scientific procedures, which are necessary for the development of an anti venom agent from plants. Considering these aspects one can say that a permanent and suitable protection against any snake bite poisoning will be fulfilled in the near future and liposomes may become the way for developing a new and effective anti snake venom dosage form.

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