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Protocol

Can Rabies Vaccine-Induced Antibodies or Intravenous Rabies Immunoglobulins Help Neutralise Snake Venoms for Early Mitigation of Snakebite-Related Toxicity?: An Exploratory Protocol

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A B S T R A C T

Many scientists are looking for ways to achieve early mitigation of snakebite toxicity to minimise death and disability caused by snake envenomation. The rabies virus glycoprotein, with homologies to snake venom/ toxins, can alter behaviour in animals through the inhibition of nicotinic acetylcholine receptors (nAChRs) present in the central nervous system. Based on this principle of homology between rabies G protein similar to snake venom toxin, there should be an experiment to analyse whether rabies antibodies (primarily against the G protein of the rabies virus) can neutralise snake venom peptides like that of alpha-bungarotoxin etc. and help mitigate snake venom-induced toxicity at the earliest.

Keywords: Snakopathy, Rabies G Protein, Snake Venom Peptides

Introduction

Snakebite is a major public health problem in India, with the majority of victims hailing from a rural agrarian population having poor access to medical facilities. Healthcare in India has, in the past few decades, witnessed considerable improvement in many indices; but snakebite continues to remain a largely neglected area. The Million Death Study reported the number of deaths due to venomous snakebites in India to be as high as 46,900 per year.[1] This is a huge number, as compared to other countries like Australia which have maintained a steady low rate for over 20 years.[2] Many scientists are looking for ways to achieve early mitigation of snakebite toxicity to minimise death and disability caused by snake venom.

Justification

Despite ongoing research on new anti-venoms and new molecules to neutralise a wide variety of venoms of different snake species, we need immediate solutions with existing drugs and molecules and anti-venoms till discoveries are put into practice. Also, current anti-venoms are in short supply[3] and not available up to the Primary Health Centre (PHC) level in rural areas where snakebite cases are attended. With the initiative of zero human rabies deaths by 2030, rabies vaccines and rabies immunoglobulins are available up to Community Health Centres and even at PHCs, where they are readily available to snakebite patients for early mitigation of snake envenomation till the patients are transported to higher centres for treatment and ventilation.

Material and Methods

From an extensive literature review, we have concluded that rabies virus-induced drastic behaviour modifications in infected hosts are due to rabies virus glycoprotein, with homologies to snake venom/ toxins, that can alter behaviour in animals through inhibition of nicotinic acetylcholine receptors (nAChRs) present in the central nervous system.[4] Neuroparalysis in neurotoxic snakes is due to the blockade of neuromuscular receptors pre- and post-synaptically in krait bites and post-synaptically in cobra bites. Irreversible binding of the toxin to pre-synaptic receptors slows down the recovery in the case of krait envenomation with the duration varying between 30 hours and 6 days.[5] A short region in the rabies virus glycoprotein's ectodomain, bearing homology to a few snake toxins, binds to the orthostatic binding site on muscle nAChRs and selectively binds to neuronal cells.[6] Based on the capacity of the peptides to compete with alpha-bungarotoxin binding to the receptor with apparent affinities similar to those of other cholinergic ligands, it is believed that loop 2 of the neurotoxins and the rabies virus glycoprotein's structurally similar segment act as recognition sites for the acetylcholine receptor.[7–9]

Rabies vaccine is primarily made of glycoprotein G[10] and rabies antibodies may have the potential to neutralise similar antigenic toxins of snake venom. Once a portion of snake venom toxin is neutralised, the whole toxin molecule would be deformed and no more would be able to bind to nAChRs. Based on this principle of homology between rabies G protein and snake venom toxin, there should be an experiment on whether rabies antibodies (primarily against G protein of rabies virus) can neutralise snake venom peptides like that of alpha-bungarotoxin etc. and help mitigate snake venom-induced toxicity early to revive the patient. There may be other toxin peptides that the rabies antibodies can bind to and neutralise. For this, both in vitro and in vivo studies need to be planned. Administration of rabies vaccine/ immunoglobulins to human patients would not be difficult as current licensed rabies vaccines/ immunoglobulins can be used to assess the impact. Recently marketed human monoclonal rabies antibody preparation[11] would be of immediate value in such cases of snake envenoming. Intravenous use of readymade rabies antibodies, i.e. Human Rabies Immunoglobulins[12] (HRIG) can be of great help in neurotoxic snake bites by elapids, especially cobra and krait and many other elapids for which antivenom is not available[13] or not effective[14]. Another strategy could be to involve the snakebite victims who have neurological signs and symptoms and may have been vaccinated before with the rabies vaccine. In remote areas where the transport of snakebite victims is difficult or very slow, the 4-site intra-dermal rabies vaccine can be administered to them as boosters[15] for rapid endogenous rabies antibody development and they can be observed for relief from venom toxins.

There could be an alternative to anti-snake venom (ASV) for places where it is ineffective or not available, especially in patients of neurotoxic envenoming globally. For this proposal, an appropriate experiment needs to be designed and implemented in designated laboratories. Another proposal is to have direct mouse inoculation tests by injecting venom and then administering rabies immunoglobulins in different doses intravenously after an hour or so to see the impact. There is homology of the glycoprotein of rabies virus and krait venom and both can be targeted by the antibodies of one another.[16] This would also help in achieving the objective of one health for the betterment of service delivery to remote areas where dog bites and snakebites are actually happening.[17]

Conclusion

This concludes that the role of anti-rabies vaccine and intravenous immunoglobulin should be explored in the neutralisation of snake venom for the early management of snakebite toxicity. If experiments are proven beneficial, then available anti-rabies preparation can avert deaths and paralysis of snake-o-pathy[18] in rural areas. In army battle conditions, using ASV for local infiltration of wild animal bite wounds may be of help to neutralise rabies virus in situ, as the army keeps vials of ASV with them but not of RIG.

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Conflict of Interest: None

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