EDITORIAL

Biomarkers in Snakebite: Will This be a Reality in Near Future?

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Snakebite is not a priority-listed disease in India. It is estimated that around 10 lakh bites occur annually, with around 58,000 reported deaths. This probably is underreporting, as many cases even do not reach hospitals. Probably 30% of cases are due to poisonous species. The affected population largely resides in rural area, where access to health care is still a challenge. This further is compounded by the non-availability of antisnake venom (ASV).[1,2]

The availability of antivenom in many countries is still a challenge. There are also issues of sensitivity reactions to ASV when administered to victims. This is further compounded by issues in diagnosing envenomation early for timely use of antivenom treatment in patients with definite envenomation.

The history, clinical signs and a series of tests are needed. Many of the tests are not available in rural settings, or do not become abnormal until the organ dysfunction has set in. The snakebite severity score (SSS) is another tool to judge severity.[3] However, the commonly used bedside 20 minute clotting test has poor diagnostic accuracy.[4]

We also know that the clinical features and laboratory investigations done to look for envenomation are seen only in established envenomation, where antivenom may be of limited or no benefit due to delay in administration. Hence, there is an urgent need to develop an early diagnostic test for envenomation at the bedside. It should be cheap and available in countries that have poor resources. In fact, many specific tests have been developed for different poisonings in the past.[5]

This further mandates early identification of envenomation to give ASV to only those with poisonous snakebite. By doing so, one can prevent neurological, hemostatic or renal complications. It has also been observed that either ASV given is deficient or in excess based on clinical treatment and whole blood clotting times.[6]

Further if one uses clotting time, one may miss the envenomation due to cobra and crait snakebite as it may be normal.

Even in resource-rich countries like Australia there is delay due to a lack of early diagnosis of systematic envenoming.[7]

Hence, there is an urgent need for developing biomarkers for early diagnosis to give ASV to only those subjects who have poisonous snakebites.

There are no protocols or guidelines from WHO, MOHFW or ICMR regarding the use of biomarkers to diagnose and treat ASV early in needy patients.[8,9]

Phospholipase A2 (PLA2) is one of the enzymes in snake venoms in most of the poisonous snakes from elapid and viperid species. Many studies have identified PLA2 activity in snake venoms, and it is now considered a standard test to confirm the presence of venom. Phospholipase A2 activity in the blood of patients with snake envenomation has also now been studied in quite a few studies.[10]

The various other enzymes, including L-amino oxidases, PLA2, serine proteinases, snake venom metalloproteinase, 5′-nucleotidase, phosphomonoesterase, and phosphodiesterase have also been found in venom gland of the genus Echis. This was shown in transcriptome analysis of venom.[10]

5′-nucleotidases are identified as one of the hydrolytic enzymes which have important role in envenomation of prey/victim. This enzyme is consistently present in all four medically significant snake species in India. 5′-nucleotidases act by preventing platelet aggregation by interaction with factor IX of the blood coagulation cascade.[11]

These enzymes in the blood of snakebite subjects also confirm envenomation and the likely need for ASV within 2–3 hours to prevent the onset of complications. In the last decade or so, quite a few studies have been done in various countries looking at these enzymes in snake venom and the blood of the victims of snakebite.

Kaulgud et al. is their study of 20 subjects found a substantial decrease in the level of PLA2 after ASV administration, and it was observed that complications were directly related to the PLA2 levels in the blood of the victims.[12]

Maduwage el al. in their study of different varieties of snakebite found snake envenomation using PLA2 assay. There was significant correlation between PLA2 activity and venom specific EIA in the sera of patients with Russell's viper envenomation ($r = 5\ 0.61$; $p - 50.0002$), hump-nosed pit viper envenomation ($r = 5\ 0.49$; $p - 50.003$) and in multiple samples from the 5 black snake envenomations ($r = 5\ 0.95$;

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p, – 0.0001) was significant. The PLA2 activity decreased markedly after ASV and increased after venom administration.[13]

Wedasingha et al. had in their study of 237 confirmed snakebite patients (Russell's viper, 72; hump-nosed viper, 80; nonvenomous snakes, 31; and unidentified bites, 54), found systemic envenoming occurred in majority. They analyzed secretory phospholipase A2 (SPLA2), neutrophil gelatinase-associated lipocalin (sNGAL) and clusterin (sCLV) and found SPLA2 to be the best predictor of systematic envenoming. Hence, one can use SPLA2 as one of the biomarkers.[14]

In the present study, authors have studied -5'nucleotidase in serum, which is one of the many enzymes present in snake venom in 82 snakebite victims. This has a high molecular mass >3 to 100 kDA. It causes inhibition of platelet aggregation through interaction with factor IX.

They measured it at admission and alter 24 hours when ASV had already been given. Significant correlation with SSS and outcome was observed. A positive correlation was observed between 5'nucleotidase levels and SSS at both 0 and 24 hours, with correlation coefficients of 0.55–0.61, respectively ($p < 0.001$). The level of 5'nucleotidase in subjects requiring dialysis, having compartment syndrome, requiring fasciotomy and mechanical ventilation correlated with severity of disease. The authors concluded it to be a reliable marker to predict severity of bite and outcome.[14] One can conclude that it can also serve as a dynamic indicator for monitoring of progression of disease and therapeutic decisions. However, having a larger sample size and diverse cohorts in future studies may validate the utility of this biomarker.[15]

There is still a need to study further these biomarkers to validate the current knowledge about utility of these in snakebite victims. Enzyme-linked immunosorbent assay (ELISA)-based measurements can be converted to point of care tests which will make it more appropriate even for remote rural areas. This will help in rationalization of the use of ASV which is again in short supply. Therefore, there is an urgent need to confirm envenomation to rationalize ASV use so as to reduce prolonged hospitalization and ICU admissions, thereby reducing cost and improving resource utilization. Albeit, it can be achieved by a biomarker test in the future.

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