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Variable efficacy of Indian polyspecific anti-snake venom against the Big Four - a major challenge to reducing snakebite mortality in India

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Indian polyspecific antivenom is primarily designed to neutralize venoms of the four major snake species responsible for more than 90% of all venomous snakebites in India. Known as the "Big Four", they include the binocellate cobra (Naja naja), common krait (Bungarus caeruleus), Russell's viper (Daboia russelii) and saw-scaled viper (Echis carinatus). Many issues relating to variations in efficacy and dosing and associated adverse effects make the Indian antivenom a less than optimal antidote. We aim to highlight the presence of a batch-to-batch variation in the clinical and pre-clinical efficacy of Indian antivenom across different manufacturers.

These findings are part of a multicenter Indian study conducted between 2013-2016, to document the geographical variation in bites by different species, confirm syndrome-species correlation and collect serum samples from snakebite victims for venom detection kit evaluation. 948 venomous bites were documented across 6 centres. A higher adjusted mortality rate was noted with particular antivenom batches used at one center. Batches were categorized into high clinical efficacy (no mortality), intermediate efficacy (13-15% mortality) and low efficacy (80% mortality). Patients treated with intermediate and low efficacy batches also had higher mean rates of dialysis, blood product support and mechanical ventilation. Based on these observations, studies on IgG F(ab')2 concentrations, binding specificities, antibody titers and lack of specific antibodies were conducted on select antivenom batches from different clinical efficacy groups.

Antivenom batches varied in total protein concentration (1.17 to 2.67 mg/ml). Antibody titers against the Big Four venoms, measured by indirect ELISA at 8 serial dilutions (1: 1000 to 1:128,000), were higher in the high efficacy batches, against all 4 snake venoms, compared to titers in the intermediate and low efficacy batches. Human serum albumin probed with antivenom samples revealed significant cross-reactivity with one intermediate efficacy batch.

Binding specificity studies of antivenom antibodies to the Big Four venom proteins, on Western blots subsequent to reducing SDS-PAGE (4-20% gels) of venom proteins, showed that none of the batches lacked antibodies against venom proteins of molecular weight >15kDa across the four species. Immune band intensities of blots probed with low / intermediate efficacy antivenom were however lower than those of blots probed with high efficacy antivenom. Venom blots probed with low-efficacy antivenom also revealed the absence antibodies to <15kDa MW venom proteins of D. russelii, B. caeruleus and E. carinatus when compared with a Ponceau-S stained SDS-PAGE of venom proteins. N-terminal sequencing of the missing proteins identified several important venom components of the three species.