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REFERENCES

1 **Warrell DA and international panel of experts**. WHO/SEARO Guidelines for the clinical management of snake bites in the Southeast Asian region. *Southeast Asian J Trop Med Public Health* 1999;**30**(suppl 1):1–85.
2 **Lewis RL**, Gutmann L. Snake venoms and the neuromuscular junction. *Semin Neurol* 2004;**24**:175–9.
3 **Riviere G**, Choumet V, Audebert F, *et al*. Effect of antivenom on venom pharmacokinetics in experimentally envenomed rabbits: toward an optimization of antivenom therapy. *J Pharmacol Exp Ther* 1997;**281**:1–8.
4 **Warrell DA**. Animal toxins. In: Cook GC, Zumla A, eds. *Manson's tropical diseases*. London: WB Saunders, 2003:581–618.
5 **Bawaskar HS**. Snake venom and antivenom: Critical supply issues. *J Assoc Physicians India* 2004;**52**:11–13.
6 **Harris JB**. Snake venoms in science and clinical medicine 3. Applied immunology in snake venom research. *Trans R Soc Trop Med Hyg* 1989;**83**:745–47.
7 **Agrawal PN**, Aggarwal AN, Gupta D, *et al*. Management of respiratory failure in severe neuroparalytic snake envenomation. *Neurol India* 2001;**49**:25–8.
8 **Bomb BS**, Roy S, Kumawat DC, *et al*. Do we need anti-snake venom for management of elapid ophitoxemia? *J Assoc Physicians India* 1996;**44**:31–3.
9 **Lalloo DG**, Trevett AJ, Korinhona A. Snake bites by the Papuan taipan (Oxyuranus scutellatus canni): Paralysis, hemostatic and electrocardiographic abnormalities and effects of antivenom. *Am J Trop Med Hyg* 1995;**52**:525–31.
10 **Tariang DD**, Philip PJ, Alexander G, *et al*. Randomized controlled trial on the effective dose of anti-snake venom in cases of snake bite with systemic envenomation. *J Assoc Physicians India* 1999;**47**:369–72.
11 **Paul V**, Pratibha S, Prahlad KA, *et al*. High-dose anti-snake venom versus low-dose anti-snake venom in the treatment of poisonous snake bites – a critical study. *J Assoc Physicians India* 2004;**52**:14–17.
12 **Warrell DA**. Crisis in snake anti-venom supply for Africa. *Lancet* 2000;**356**:2104.
13 **Theakston RDG**, Fan HW, Warrell DA, *et al*. *Am J Trop Med Hyg* 1992;**47**:593–604.
14 **Smalligan R**, Cole J, Brito N, *et al*. Crotaline snake bite in the Ecuadorian Amazon: randomised double blind comparative trial of three South American polyspecific antivenoms. *Br Med J* 2004;**329**:1129–36.
15 **Theakston RDG**, Warrell DA, Griffiths E. Report of a WHO workshop on the standardization and control of antivenoms. *Toxicon* 2003;**41**:541–57.

COMMENTARY

Snake antivenom research: the importance of case definition

G K Isbister

Snake envenoming is a major public health issue in the rural tropics, with large numbers of envenomings and deaths.[1 2] However, there continues to be limited evidence on the clinical features, epidemiology, and treatment of these patients.[1 2] In some parts of the world, there is a continuing shortage of antivenom.[3] Agarwal *et al* [4] attempt to answer a pertinent clinical question in their region. The study aims to justify a reduced dose of antivenom (thus reducing cost of treatment) in their hospital and surrounding regions. However, while the study provides useful insight into the issues of snakebite management in the tropics, there are a number of problems with the design, and the study cannot be generalized to other parts of the world. The appropriate design for the study would be a randomised, controlled trial (RCT), but these are not often undertaken because of the difficulties with RCT in this setting and the resources needed to measure venom concentrations in envenomed patients.

RCTs of antivenom are difficult to undertake for a number of reasons. The clear efficacy in many cases makes it unethical to perform placebo RCTs. It is possible to perform comparison RCTs of different antivenoms or comparison of different dosing regimens.[5–7] A more significant problem is making sure that controlled trials include only definite cases of snake envenoming, and that a known and relatively homogenous type and severity of envenoming is being studied, so that results are not biased. An RCT of scorpion antivenom in Tunisia,[8] which showed no benefit of antivenom, has been criticized because it included only a small number of severely envenomed patients, the group most likely to benefit from antivenom.[9]

Clinical toxinology has been plagued by poor case definition,[10] leading to the erroneous association of many clinical syndromes with particular venomous or poisonous animals.[11] This creates problems when undertaking clinical trials in clinical toxinology because if the study includes other than definite cases, it is difficult to determine what is the treatment effect. This is a significant problem in the study by Agarwal *et al*. Their study included any patients with ''severe neurotoxic envenoming'' who required mechanical ventilation, and not snake bites that caused neurotoxicity (requiring mechanical ventilation) and for which their was a definite species identifcation. This meant that the study included two very different types of snakes (cobras and kraits) without being able to identify within the study which patients were bitten by which snake.

The response of neurotoxicity to snake antivenom is dependent on the type of neurotoxins the snakes possess.[1 12] Cobra venom contains mainly post-synaptic neurotoxins, which have a curare-like effect and can be reversed by snake antivenom after clinical effects have developed. Conversely, krait venom contains many presynaptic neurotoxins, which are not reversible once paralysis has developed and so respond poorly to delayed antivenom.[1 12] The study by Agarwal *et al* therefore contains an unknown proportion of cases that may respond well to antivenom (cobra bites) and an unknown proportion that are unlikely to respond to antivenom (krait bites). In three cases, dead snakes were collected, demonstrating that both snake types were included in the study. Because their study was not randomized and followed a ''before and after'' design, an increase in the proportion of cobra bites over time could have resulted in the low dose (''after'') group being inherently more likely to respond to antivenom than the high dose (''before'') group. Even if the study was randomized, if both groups were predominantly krait bites and unlikely to benefit from antivenom, then there

would be little difference between groups, but any beneficial effect of the higher antivenom dose for the smaller proportion of cobra bites would have been masked. Therefore, even in the setting of the authors' own hospital, their results should be seen only as a useful exploratory investigation or pilot study for future more rigorous study designs.

The reason that case definition is problematic in most studies is the difficulty involved in defining definite bites and establishing the exact species/group involved.[9] Snakes are not caught or collected in many cases, as seen in this report, although this study had a particularly low rate of snake capture (3 out of 55). The other method of snake identification is using an ELISA to detect snake venom in patient blood.[13] One disadvantage of this method is that there may be significant cross reactivity, but this is unlikely to be a problem with distinguishing different genera of snakes such as cobras (*Naja* spp.) and kraits (*Bungarus* spp.). The other problem is the cost and access to such testing, as stated by Agarwal *et al*. However, there is a difference between ''point of care'' venom detection kits, such as those used in Australia,[14] and the collection and storage of samples for research that can be sent to distant laboratories to be analysed. The latter is certainly possible in the rural tropics by collaboration with international research groups. This has been carried out in many parts of the developing world,[13] including Sri Lanka, with similar snakes.[15] The major advantage of ELISA is that serial venom concentrations can be quantified, which will allow an accurate determination of antivenom dose required.[13] Such studies with definite case inclusion are desperately required to improve antivenom treatment for snake envenoming.

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REFERENCE

1 **White J**, Warrell D, Eddleston M, *et al*. Clinical toxinology–where are we now? *J Toxicol Clin Toxicol* 2003;**41**:263–76.
2 **Chippaux J-P**. Snake-bites: appraisal of the global situation. *Bull World Health Organ* 1998;**76**:515–24.
3 **Theakston RDG**, Warrell DA. Crisis in snake antivenom supply for Africa. *Lancet* 2000;**356**:2104.
4 **Agarwal R**, Aggarwal A N, Gupta D, Behera D, Jindal S K. Low dose of anti-snake venom is as effective as high dose in patients with severe neurotoxic snake envenoming. *Emerg Med J* 2005;**22**:397–9.
5 **Smalligan R**, Cole J, Brito N, *et al*. Crotaline snake bite in the Ecuadorian Amazon: randomised double blind comparative trial of three South American polyspecific antivenoms. *BMJ* 2004;**329**:1129.
6 **Caovilla JJ**, Barros EJ. Efficacy of two different doses of antilonomic serum in the resolution of hemorrhagic syndrome resulting from envenoming by Lonomia obliqua caterpillars: a randomized controlled trial. *Toxicon* 2004;**43**:811–18.
7 **Ariaratnam CA**, Sjostrom L, Raziek Z, *et al*. An open, randomized comparative trial of two antivenoms for the treatment of envenoming by Sri Lankan Russell''s viper (Daboia russelii russelii). *Trans R Soc Trop Med Hyg* 2001;**95**:74–80.
8 **Abroug F**, Elatrous S, Nouira S, *et al*. Serotherapy in scorpion envenomation: a randomised controlled trial. *Lancet* 1999;**354**:906–9.
9 **Isbister GK**, Graudins A, White J, *et al*. Antivenom treatment in arachnidism. *J Toxicol Clin Toxicol* 2003;**41**:291–300.
10 **Isbister GK**. Data collection in clinical toxinology: debunking myths and developing diagnostic algorithms. *J Toxicol Clin Toxicol* 2002;**40**:231–7.
11 **Isbister GK**. Necrotic arachnidism: the mythology of a modern plague. *Lancet* 2004;**364**:549–53.
12 **White J**. Elapid snakes. In: Dart RC, ed. *Medical toxicology*. Philadelphia: Lippincott Williams & Wilkins, 2004:1566–78.
13 **Theakston RD**. An objective approach to antivenom therapy and assessment of first-aid measures in snake bite. *Ann Trop Med Parasitol* 1997;**91**:857–65.
14 **Jelinek GA**, Tweed C, Lynch D, *et al*. Cross reactivity between venomous, mildly venomous, and non-venomous snake venoms with the Commonwealth Serum Laboratories Venom Detection Kit. *Emerg Med Australas* 2004;**16**:459–64.
15 **Theakston RD**, Phillips RE, Warrell DA, *et al*. Envenoming by the common krait (Bungarus caeruleus) and Sri Lankan cobra (Naja naja naja): efficacy and complications of therapy with Haffkine antivenom. *Trans R Soc Trop Med Hyg* 1990;**84**:301–8.