Intensive Care Med (2009) 35:1532–1538
DOI 10.1007/s00134-009-1556-7

ORIGINAL

Simon G. A. Brown
Ngaire Caruso
Meredith L. Borland
David L. McCoubrie
Antonio Celenza
Geoffrey K. Isbister

Clotting factor replacement and recovery from snake venom-induced consumptive coagulopathy

Received: 3 August 2008
Accepted: 28 April 2009
Published online: 23 June 2009
© Springer-Verlag 2009

On behalf of the ASP investigators.

This article is discussed in the editorial available at:
doi:10.1007/s00134-009-1557-6.

S. G. A. Brown · A. Celenza
Discipline of Emergency Medicine, University of Western Australia, Crawley, WA, Australia

S. G. A. Brown · N. Caruso
Department of Emergency Medicine, Fremantle Hospital, Fremantle, WA, Australia

M. L. Borland
Department of Emergency Medicine, Princess Margaret Hospital for Children, Subiaco, WA, Australia

S. G. A. Brown (✉) · D. L. McCoubrie
Department of Emergency Medicine, Royal Perth Hospital, GPO Box X2213, Perth, WA 6001, Australia
e-mail: simon.brown@uwa.edu.au

A. Celenza
Department of Emergency Medicine, Sir Charles Gairdner Hospital, Nedlands, WA, Australia

G. K. Isbister
Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia

G. K. Isbister
Calvary Mater Hospital, Newcastle, NSW, Australia

Abstract *Introduction:* Using clotting factors (fresh frozen plasma and/or cryoprecipitate) to treat snake venom-induced consumptive coagulopathy (VICC) is controversial. We aimed to determine if factor replacement after antivenom is associated with an earlier return of coagulation function. *Methods:* We retrospectively analysed VICC cases due to brown snake (genus *Pseudonaja*), tiger snake (*Notechis*, *Tropidechis*, and *Hoplocephalus*), and taipan (*Oxyuranus*) envenoming. Recovery of international normalized ratio (INR)/prothrombin time (PT) was compared between patients who did not receive factor replacement and those who did, and between patients who received factor replacement $\leq$ 4 h of commencing antivenom and those who received factor replacement later or not at all. *Results:* There was no significant difference between cases receiving clotting factors and cases that did not, however in 21 cases having factor replacement within 4 h, the median time to coagulation recovery was 4.6 h (interquartile range [IQR] 3.5–8.8), versus 9.5 h (IQR 7.3–13) in 106 cases who had clotting factors later or not at all ($P < 0.001$). No serious adverse effects attributed to clotting factors were recorded. Recovery by 6 h after starting antivenom was also more likely in those who were younger, in tiger snake envenoming, and where the interval between bite and starting antivenom was longer. The initial dose of antivenom did not appear to influence the likelihood of recovery at 6 h. *Conclusion:* Early factor replacement after antivenom is associated with earlier improvement of coagulation function. Randomised controlled clinical trials to determine the efficacy and safety of factor replacement for VICC after venom neutralisation are required.

Keywords Envenoming · Snake · Antivenom · Fresh frozen plasma · Cryoprecipitate

Background

Venom-induced consumptive coagulopathy (VICC) is characterised by unrecordable clotting parameters and elevated cross-linked fibrinogen degradation products (XL-FDP)/D-dimers and is the most common manifestation of Australasian elapid snake envenoming [1]. VICC is also an important cause of morbidity and death in the rural tropics, where hundreds of thousands of people die from snakebite every year [2]. Three of the five major groups of Australasian elapid snakes, including brown snakes (*Pseudonaja*), taipans (*Oxyuranus*), and the tiger snake group (*Notechis*, *Tropidechis*, and *Hoplocephalus*) cause VICC [3–6]. The venoms of these snakes contain similar prothrombin activators that cause complete defibrination and incoagulable blood [7]. The coagulation defects seen in cases of envenoming by each of the above species include consumption of fibrinogen, factor V, factor VIII, and partial consumption of prothrombin. There is less effect on the remaining coagulation factors and platelets [4–6]. Antivenoms (AV) are available to neutralize these toxins, after which clotting function presumably recovers by synthesis of new clotting factors [4, 8].

The use of clotting factor replacement for VICC has been controversial because of fears that this may worsen the coagulopathy by providing more substrate [9, 10]. A previous canine study has claimed that fresh frozen plasma (FFP) may worsen coagulopathy and cause death after brown snake envenoming [9]; however, the number of dogs studied was small, the methodology was suboptimal, and the conclusions were heavily criticised [10]. FFP is the most available product and contains the important factors that require replacement in VICC—fibrinogen, factor V, and factor VIII. Although cryoprecipitate is a better source of fibrinogen, it is not clear whether this is the most important factor required for recovery. There have been no trials of factor replacement for VICC in humans and only scattered case series and case reports of its use [11–13].

FFP has been a routine treatment for VICC in Australian intensive care units. However, since 2003 we have noted a shift in treatment patterns in the form of higher antivenom doses and infrequent FFP use (< 5% of cases) [8]. This change may be because of data suggesting that higher doses of antivenom might be required [14], combined with ongoing controversy over FFP treatment in the presence of inadequate venom neutralisation [9, 10, 15].

Study aims and hypotheses

By examining cases managed before 2003, when clotting factor replacement was near universal, and more recent cases, when the majority were managed without factor replacement, we aimed to determine whether factor replacement after antivenom is associated with an earlier return of coagulation function. Without FFP, the median time from antivenom to return of coagulation function, defined by an international normalized ratio (INR) of less than 2.0, is 9.2 h [8]. Our primary hypothesis was that early initiation of clotting factors within 4 h of starting antivenom would be associated with an earlier return of clotting function. We also aimed to identify any other clinical features and treatments, specifically antivenom dose, associated with earlier recovery.

Methods

Design and ethical approval

We retrospectively analysed VICC cases due to brown snake (genus *Pseudonaja*), tiger snake group genera (*Notechis*, *Tropidechis* and *Hoplocephalus*), and taipan (genus *Oxyuranus*) envenoming. The Australian Snakebite Project (ASP) is an ongoing multicentre prospective observational study that recruits snake bite cases presenting to over 60 tertiary and regional Australian hospitals and all major poison information centres. We have obtained ethics approval for all institutions involved. ASP cases recruited between July 2003 and June 2006 were included in this analysis. A standardized study datasheet was completed by the treating physician and included the data used in this analysis.

Additional retrospective cases of snakebite treated in Western Australia teaching hospitals from December 1991 to December 2004 were identified by contacting the authors of previous retrospective studies and performing chart audits at the relevant institutions. These cases had been identified by multipronged strategies using International Classification of Diseases (ICD)-9 and ICD-10 coding, hospital pharmacy records of antivenom use, and laboratory records of Venom Detection Kit (VDK) (CSL, Melbourne, Australia) results and abnormal coagulation results. Ethics approval for the retrospective chart review was granted by the Human Research Ethics Committee (HREC) of the South Metropolitan Area Health Service (WA). A single trained investigator (NC) abstracted data directly from hospital clinical and laboratory records. Cases were excluded if essential data were missing.

Inclusion criteria

We included cases if they developed VICC and received treatment with antivenom for brown snake, tiger snake (or related snakes), or taipan envenoming. VICC was defined by elevated D-dimers (if available) plus coagulopathy diagnosed by an INR of more than 2.0; a prothrombin

time (PT) of more than 24 sec, if an INR result was not available, or unclottable blood by 20 min as measured by a whole blood clotting time (WBCT) in a glass vial, if treatment was initiated in a hospital without access to clotting studies. "Severe coagulopathy" was defined by an INR of more than 7 or a PT of more than 60 at any stage, on the basis that these were the values above which laboratories begin to report "unrecordable" values.

Primary and secondary outcomes

The primary outcome was the time interval from initiation of the first dose of AV to recovery defined by a reduction in the INR to 2.0 or less (or PT $\leq$ 24 sec if the INR was not available), based on a previous study of clotting recovery in VICC [8]. Secondary outcomes were time interval to recovery of the activated partial thromboplastin time (APTT), defined as less than 100 s and time interval to recovery of fibrinogen, defined as more than 0.5 mg/dL. These secondary outcome cutoffs were chosen because all laboratories that analysed specimens were able to report values below and above these values, respectively. We also compared the number of bleeding complications between groups, classified as either "major" (involving the brain or requiring resuscitation) or "other."

Statistical analysis

We compared those who did not receive factor replacement at any time with those who did, and those who received factor replacement early (within 4 h of initiating antivenom) with those who received factor replacement late (after 4 h) or not at all. In those for whom FFP was started within 4 h, we also examined time to recovery against the number of units started in the first 4 h. In one child who received FFP, this was corrected to an adult dose by assuming that 10 mL/kg to 15 mL/kg of FFP was equivalent to an adult dose of 4 units.

A dichotomous endpoint of coagulation recovery (INR $\leq$2 or PT $\leq$24) at 6 h after starting antivenom was then used to perform a backward stepwise logistic regression analysis of association between outcome and variables sex, age, snake species group, interval from bite to commencing antivenom, initial dose of antivenom defined as the number of vials started in the first hour, and administration of clotting factors within 4 h of antivenom. To detect any potential differences in timing of coagulation studies between groups that might have biased this analysis, we compared the median time intervals from starting antivenom to the last set of coagulation studies within the following 6 h.

Statistical analysis was performed using Stata version 10 for windows (StataCorp LP, College Station, Texas). The chi-square and Fisher exact tests were used to compare dichotomous data and the Mann–Whitney test was used to compare time interval data. We defined statistical significance as a P value of less than 0.05. Spearman rank correlation was used to assess the relationship between initial FFP dose and time to recovery. The binomial method was used to calculate confidence intervals for proportions.

Results

Sixty-three cases satisfying our inclusion criteria were available from the prospective ASP study and 70 cases were retrospectively identified from WA (Fig. 1). In 11 cases, initial diagnosis was based on a bedside WBCT, all of which later had clear evidence of VICC when formal laboratory bloods were taken, including 8 who had not yet reached the primary endpoint. One prospective ASP case died before coagulation recovery and could not be included in the primary outcome analysis of return of clotting function; however, because 6 h results were available, was included in the logistic regression analysis. Six cases (including 2 deaths) from the retrospective cohort were excluded from analysis because of missing treatment information and/or laboratory results.

The primary analysis of time to recovery thus included 126 cases; 71 who did not receive factor replacement and 55 who received factor replacement, of which 21 had this commenced within 4 h of antivenom The logistic regression analysis of clotting function at 6 h was able to include 127 cases.

Baseline characteristics were comparable between groups except that those who did not receive factor replacement were more likely to have a higher initial dose of antivenom (median 3 vials [interquartile range (IQR) 2–4] versus median 1 vial [IQR 1–2], $p = 0.0001$). There were no taipan bites in the factor replacement group.

Fifty-three cases received FFP (median dose 4 units, IQR 2–6 units, range 1–18 units) and 26 received cryoprecipitate (median dose 8 units, IQR 8–8 units, range 4–32 units). In the 21 cases where factor replacement was initiated within 4 h of antivenom, FFP alone was used in 16, FFP plus cryoprecipitate in 4, and cryoprecipitate in 1.

A comparison between those who received no clotting factors and those who received clotting factors at any time found no statistically significant difference in any endpoint.

A comparison of the group receiving clotting factors for 4 h or less versus those who received clotting factors for more than 4 h or not at all is presented in Table 1. Clotting recovery was significantly faster in the $\leq$4 h group by all parameters studied. Baseline characteristics and timing of coagulation studies relative to the

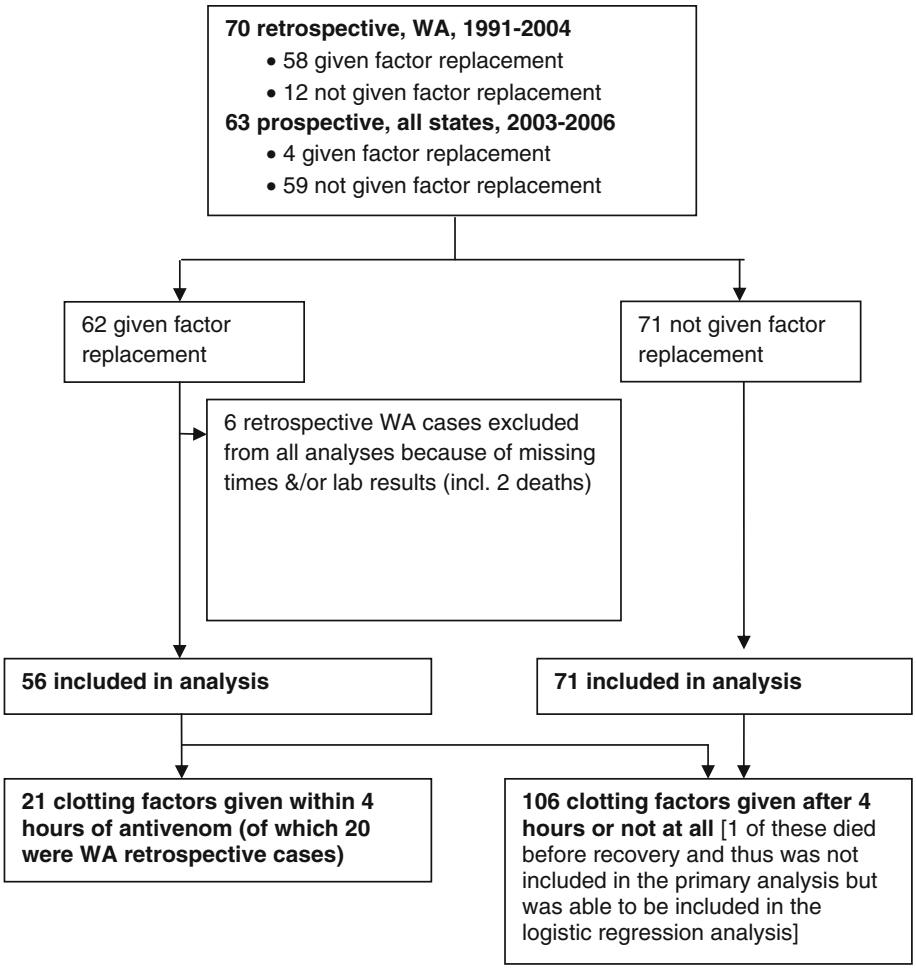

Fig. 1 Study flow diagram

Table 1 Baseline characteristics and outcomes

	CF given > 4 h after AV or not at all $n = 106$	CF given ≤ 4 h of AV $n = 21$	
Male	79 (75%)	15 (71%)	
Age in years (mean [SD])	37 (20)	36 (18)	
Snake			
Brown	67 (63%)	15 (71%)	
Tiger	31 (29%)	5 (24%)	
Taipan	4 (3.7%)	0	
Unknown	4 (3.7%)	1 (5%)	
Severe coagulopathy	83 (78%)	18 (86%)	
Thrombocytopenia (<150)	45 (43%)	10 (48%)	
Hours from snake bite to AV	3.5 (1.9–5.3)	3.2 (1.8–4.7)	
Number of AV vials first hour	2 (1–4)	2 (1–2)	
Hours from AV to last coagulation studies in the 6 h after AV	4.5 (3.3–5.3)	4.8 (4.1–5.4)	
Hours from AV to recovery of INR/PT	9.5 (7.3–13)	4.6 (3.5–8.8)	$p < 0.001$
Number improved by 6 h (%, 95% CI)	17 (16%, 9.6–24%)	14 (67%, 43–85%)	$p < 0.001$
Hours from AV to APTT <100 s	6.5 (4.3–9.2)	4.0 (1.4–5.3)	$p = 0.002$
Hours from AV to fibrinogen >0.5 mg/dL	10.7 (7.5–14.3)	8.0 (4.2–12.1)	$p = 0.0184$

Unless otherwise specified, values are presented as median (IQR)
CF clotting factors, *AV* antivenom, INR international normalized ratio, APTT activated partial prothrombin time

Table 2 Logistic regression analysis for association of variables with recovery of INR/PT at 6 h

	Odds ratio	95% CI	P
Clotting factor replacement within 4 h of AV	43.2	9.2–203	<0.001
Age (years)[a]	0.95	0.92–0.98	0.001
Time from bite to giving AV (hours)[a]	1.35	1.12–1.62	0.001
Tiger snake envenoming	4.98	1.43–17.4	0.012
Number of vials of AV started in the first hour of treatment[a]	1.22	0.91–1.66	0.187
Severe coagulopathy	0.39	0.10–1.45	0.158

AV antivenom

[a] The odds ratio for age, time from bite to AV and number of vials refers to the odds ratio associated with each 1 year, 1 h, and 1 vial increment, respectively

dichotomous outcome for logistic regression analysis did not vary significantly between groups.

Logistic regression analysis found that early clotting factor replacement, younger age, tiger snake envenoming, and a longer interval from bite to commencing antivenom treatment increased the likelihood of recovery by 6 h (Table 2). Further analysis of tiger snake versus brown snake cases found the median times from antivenom to recovery were 8.2 h (IQR 6.1–11.7) and 10.5 h (IQR 7.5–13.5), respectively when early FFP was not given. For the logistic regression analysis FFP and cryoprecipitate administration were not entered independently because of the small numbers receiving the later. The number of units of FFP given in the first 4 h after initiating antivenom had a significant effect on the likelihood of recovery at 6 h; all 7 patients given 4 units had recovered, versus 6 out of 13 receiving 2 or 3 units (Spearman $P = 0.0273$ for time to recovery). All 5 cases receiving cryoprecipitate had recovery at 6 h, however the sample was too small to enable further analysis of this intervention.

Bleeding of any severity was noted in 11out of 21 (52%, 95% CI 30–74%) of those receiving clotting factors within 4 h versus 34 out of 106 (32%, 95% CI 23–42%) in the remainder. Major bleeding was noted in 2 out of 21 (9.5%, 95% CI 1.1–30%) and 3 out of 106 (2.9%, 95% 0.6–8.0%), respectively. Three deaths (14%, 95% CI 3.0–36%) occurred in the early clotting factor group (1 due to hypoxic-ischaemic cerebral insult from cardiac arrest prehospital, 2 from fatal intracerebral bleeding) versus 2 (1.9, 95 0.2–6.6%) in the remainder (1 due to hypoxic–ischaemic cerebral damage and the other associated with multiple internal haemorrhages). None of these between group differences reached statistical significance. Overall, including all cases excluded from the primary analysis, the death rate was 7out of 133 (5%, 95% CI 2.1–11%).

In the 55 cases receiving clotting factors, 3 (5.5%, 95% CI 1.1–15%) had adverse events recorded that were possibly related to factor replacement. Using the number of units of FFP given as denominator (237 units) this equated to a risk per unit of FFP given of 1.2% (95% CI 0.26–3.6%). These were:

1. An episode of noncardiogenic pulmonary oedema, hypoxaemia, and rigors approximately 1 h after 4 units of FFP. The patient was treated with intravenous frusemide and oxygen and there was prompt resolution of symptoms without any need for ventilator support. The aetiology of the adverse event was not clear. No further investigations were performed to support a diagnosis of TRALI (Transfusion related acute lung injury).
2. A confluent rash of the upper arms and flanks developing after the fourth unit of FFP and;
3. A generalised rash with angioedema treated with adrenaline, occurring immediately after 4 units of FFP but also within 35 min of an 8-unit cryoprecipitate infusion and within 110 min of 5 vials of brown snake antivenom (the last in a series of doses totaling 22 vials of brown snake antivenom). No febrile reactions were identified from the case records.

Discussion

The early use of FFP within 4 h of starting antivenom treatment is associated with an earlier return of clotting function in patients with VICC after bites by Australian Elapid snakes. The proportion that had recovered was higher in those who received an initial FFP dose of at least 4 units. Those who were younger, had tiger snake envenoming, and in whom the interval between the bite and starting antivenom treatment was longer were also more likely to have recovery of INR/PT at 6 h. The initial dose of antivenom did not appear to influence recovery. The rate of serious adverse effects from FFP appeared to be low and the 95% confidence intervals overlapped with rates reported by haemovigilance programs [16, 17].

Antivenom dosing has been controversial. A retrospective study of antivenom dosing for brown snake VICC treated in Western Australia between 1991 and 2001 found that relatively large doses of antivenom (up to 22 vials) were given over the course of treatment and that clotting factors (FFP and/or cryoprecipitate) were given in

all cases although the timings of these interventions were not reported [14]. Our findings that higher doses of antivenom had no association with recovery but that early clotting factors are associated with an early return of clotting function are consistent with our previous demonstration that just 1 vial of antivenom should bind and neutralise all circulating venom in patients with severe brown snake envenoming [18]. The association between tiger snake envenoming and higher likelihood of recovery at 6 h may be because the prothrombin activators in tiger snake venoms differ to those in brown snake venoms. The finding that a longer interval from bite to antivenom treatment increases the odds of recovery by 6 h suggests a degree of spontaneous recovery due to resynthesis of clotting factors in at least some people. This may also be due to less severe or less obvious envenoming associated with delayed diagnosis and treatment.

Being nonrandomised, this study demonstrates associations only, hence, there may be other potential explanations of the results. In particular, the overrepresentation of brown snake and tiger snake envenoming treated with FFP in one geographical region (Western Australia) and at an earlier time than the prospectively collected cases introduces potential biases because of unmeasured differences between groups such as venom characteristics and treatment differences. Although reliant on retrospective data collection for most cases receiving clotting factors, the main variables, timings, treatments and endpoints (laboratory results) were objective and we found the timing of key assays before the 6 h outcome to be comparable between groups. Another issue is that standard clotting function tests and our selected cutoff for defining recovery may not be the best correlate with risk of clinically significant bleeding. Nevertheless these simple measures are useful indicators of the recovery process and are thus useful for comparing treatment groups and identifying the factors that may influence recovery [8].

Variability in FFP and/or cryoprecipitate timing, dosing, and infusion regimens was another confounder and the higher (albeit not statistically significant) rates of bleeding in the early clotting factor group suggest that early clotting factor treatment was more likely to be given to patients with bleeding. However, this association may also emphasise the improvement in coagulation that is associated with early factor replacement. The small numbers of patients receiving cryoprecipitate within 4 h in addition to FFP also meant that it was impossible to determine whether the administration of cryoprecipitate was associated with an increased likelihood of recovery at 6 h.

The low incidence of death and serious haemorrhage in our study is consistent with data available from a variety of snake bites that cause VICC [12, 19–21]. Thus, a very large randomised controlled trial would be needed to determine the mortality and morbidity effects of routine clotting factor treatment of VICC. However, smaller trials using recovery of coagulation function and adverse reactions as endpoints may help to inform clinical decision making for patients with VICC and active, potentially life-threatening haemorrhage. A number of randomised controlled trials of clotting factor replacement in VICC are required because treatment options available between and within different countries, nature of the coagulopathy, potential for ongoing venom absorption, and mortality risk from VICC may vary between snake species and geographical regions.

Acknowledgment We thank Dr. Nicole Staples (Haematologist, Royal Perth Hospital) for her review and helpful comments on the manuscript.

SGAB is supported by National Health and Medical Research Council (NHMRC) Career Development Award 513901 and GKI is supported by NHMRC Career Development Award 300785. The analysis and write-up was also supported in part by NHMRC Project Grant 490305. There was no industry funding of this project.

Ethics approval has been granted for all institutions involved in the prospective recruitment of cases to ASP. Ethics approval for the retrospective chart review was granted by the Human Research Ethics Committee (HREC) of the South Metropolitan Area Health Service (Western Australia).

Conflict of interest statement Nothing to declare.

Appendix

This manuscript is written on behalf of the ASP clinical investigators who manage recruitment at the following hospitals: Yusuf Nagree (Armadale Hospital), Michael Taylor (Bendigo Hospital), Conrad Macrokanis (Broome Hospital), Gary Wilkes and Adam Coulson (Bunbury Hospital), Chris Barnes (Bundaberg Hospital), Mark Little (Caboolture Hospital), Robert Bonnin, Richard Whitaker and Lambros Halkidis (Cairns Base Hospital), Geoff Isbister (Calvary Mater Newcastle Hospital), Nicholas Buckley (Canberra Hospital), Alan Tankel (Coffs Harbour Base Hospital), Randall Greenberg (Dubbo Base Hospital), Simon Brown (Fremantle Hospital), David Spain (Gold Coast Hospital), Kate Porges (Gosford and Wyong Hospitals), Mark Miller (John Hunter Hospital), Chris Gavaghan (Lismore Base Hospital), Anna Holdgate (Liverpool Hospital), Kent McGregor (Logan Hospital), Todd Fraser (Mackay Hospital), Peter Garrett, Mark Coghlan and Tanya Georgia (Nambour Hospital), Andrew Parkin and Colin Page (Princess Alexandria Hospital), Paul Davies (Rockhamptom Hospital), Rod Ellis (Rockingham Hospital), Bart Currie (Royal Darwin Hospital), Ken Winkel (Royal Melbourne Hospital), Justin Yeung and David McCoubrie (Royal Perth Hospital), Mark Monaghan and Mark Little (Sir Charles Gairdner Hospital), Chris Trethewy, Nick Ryan and John Kennedy (Tamworth Hospital), Peter

Miller and Katie Mills (Toowoomba Hospital), Shane Curran (Wagga Base Hospital), Naren Gunja (Westmead Hospital), Julian White (Women's and Children's Hospital, Adelaide) and the ASP data coordinator Ellen MacDonald, Fremantle Hospital. We also acknowledge the assistance of the Australian poison information centres and clinical toxicologists and many other nurses, doctors and laboratory staff who assisted with recruiting patients and collecting samples. Dr Justin Yeung and Dr Jason Scop provided a list of snakebite cases treated in WA Teaching hospitals from December 1991 to December 2005. We thank Dr Nicole Staples (Haematologist, Royal Perth Hospital) for her input during manuscript preparation.

References

1. Isbister GK, Brown SG, MacDonald E, White J, Currie BJ (2008) Current use of Australian snake antivenoms and frequency of immediate-type hypersensitivity reactions and anaphylaxis. Med J Aust 188:473–476
2. White J, Warrell D, Eddleston M, Currie BJ, Whyte IM, Isbister GK (2003) Clinical toxinology–where are we now? J Toxicol Clin Toxicol 41:263–276
3. Masci PP, Rowe EA, Whitaker AN, de Jersey J (1990) Fibrinolysis as a feature of disseminated intravascular coagulation (DIC) after *Pseudonaja textilis* envenomation. Thromb Res 59:859–870
4. Lalloo DG, Trevett AJ, Owens D, Lalloo DG, Trevett AJ, Owens D (1995) Coagulopathy following bites by the Papuan taipan (*Oxyuranus scutellatus canni*). Blood Coagul Fibrinolysis 6:65–72
5. Parkin JD, Ibrahim K, Dauer RJ, Braitberg G (2002) Prothrombin activation in eastern tiger snake bite. Pathology 34:162–166
6. White J, Duncan B, Wilson C, Williams V, Lloyd J (1992) Coagulopathy following Australian elapid snakebite: a review of 20 cases. Recent Advances in Toxinology Research Singapore: Venom and Toxin Research Group, National University Singapore, pp 337–344
7. St Pierre L, Masci PP, Filippovich I, Sorokina N, Marsh N, Miller DJ, Lavin MF (2005) Comparative analysis of prothrombin activators from the venom of Australian elapids. Mol Biol Evol 22:1853–1864
8. Isbister GK, Williams V, Brown SGA, White J, Currie BJ (2006) Clinically applicable laboratory end-points for treating snakebite coagulopathy. Pathology 38:568–572
9. Jelinek GA, Smith A, Lynch D, Celenza A, Irving I, Michalopoulos N, Erber W, Joske DJ (2005) The effect of adjunctive fresh frozen plasma administration on coagulation parameters and survival in a canine model of antivenom-treated brown snake envenoming. Anaesth Intensive Care 33:36–40
10. Tibballs J (2005) Fresh frozen plasma after brown snake bite: helpful or harmful? Anaesth Intensive Care 33:13–15
11. Porath A, Gilon D, Schulchynska-Castel H, Shalev O, Keynan A, Benbassat J (1992) Risk indicators after envenomation in humans by *Echis coloratus* (mid-east saw scaled viper). Toxicon 30:25–32
12. Warrell DA, Davidson N, Greenwood BM, Warrell DA, Tomkins A, Tugwell P, Zalin A, Bryceson AD, Parry EH, Brueton M, Duggan M, Rajković AD (1977) Poisoning by bites of the saw-scaled or carpet viper (*Echis carinatus*) in Nigeria. Q J Med 46:33–62
13. White J (2005) Snake venoms and coagulopathy. Toxicon 45:951–967
14. Yeung JM, Little M, Murray LM, Jelinek GA, Daly FF (2004) Antivenom dosing in 35 patients with severe brown snake (*Pseudonaja*) envenoming in Western Australia over 10 years. Med J Aust 181:703–705
15. Jelinek GA, Smith A, Lynch D, Celenza A, Irving I, Michalopoulos N, Erber W, Joske DJ (2005) FFP after brown snake envenoming: think twice. Anaesth Intensive Care 33:542–543
16. National Haemovigilance Programme (2006): annual report. Wellington, New Zealand Blood Service, available online at http://www.nzblood.co.nz/?t=123 Accessed 13 April 2008
17. Engelfriet CP, Reesink HW, Henn G, Mayr WR (2006) Haemovigilance. Vox Sang 90:207–241
18. Isbister GK, O'Leary MA, Schneider JJ, Brown SGA, Currie BJ (2007) Efficacy of antivenom against the procoagulant effect of Australian brown snake (*Pseudonaja* sp.) venom: in vivo and in vitro studies. Toxicon 49:57–67
19. Reid HA, Thean PC, Chan KE, Baharom AR (1963) Clinical effects of bites by Malayan viper (*Ancistrodon rhodostoma*). Lancet 7282:617–621
20. Lalloo DG, Trevett AJ, Korinhona A, Nwokolo N, Laurenson IF, Paul M, Black J, Naraqi S, Mavo B, Saweri A et al (1995) Snake bites by the Papuan taipan (*Oxyuranus scutellatus canni*): paralysis, hemostatic and electrocardiographic abnormalities, and effects of antivenom. Am J Trop Med Hyg 52:525–531
21. Malik GM (1995) Snake bites in adults from the Asir region of southern Saudi Arabia. Am J Trop Med Hyg 52:314–317