

Failure of antivenom to improve recovery in Australian snakebite coagulopathy

G.K. ISBISTER^{1,2}, S.B. DUFFULL³ and S.G.A. BROWN^{4,5}; FOR THE ASP INVESTIGATORS

From the ¹Tropical Toxinology Unit, Menzies School of Health Research, Charles Darwin University, Darwin, ²Department of Clinical Toxicology and Pharmacology, Calvary Mater Hospital, Newcastle, New South Wales, Australia, ³School of Pharmacy, University of Otago, Dunedin, New Zealand, ⁴Centre for Clinical Research in Emergency Medicine, Western Australian Institute for Medical Research and The University of Western Australia Centre for Medical Research and ⁵Discipline of Emergency Medicine, University of Western Australia, Royal Perth Hospital, Perth, Australia

Received 24 November 2008 and in revised form 4 June 2009

Summary

Background: Venom-induced consumption coagulopathy (VICC) is an important feature of snake envenoming.

Aim: To investigate the effect of antivenom and fresh frozen plasma (FFP) on recovery of VICC in Australian elapid snake envenoming.

Design: Prospective cohort study.

Methods: Patients with VICC were included from the Australian Snakebite Project (ASP). Time to recovery of VICC (defined as time until INR <2) was investigated using a time to event analysis in WinBUGS. The model considered the effects of age, sex, snake type, time of antivenom after bite, antivenom dose and use of FFP within 4 h.

Results: The study included 167 cases of VICC, median age being 41 [interquartile range (IQR): 28–53] years, and 130 (78%) were males.

Antivenom was administered at a median of 3.6 (IQR: 2.2–5.6) h after the bite at a median dose of four vials (IQR: 2–6 vials). Thirteen patients received FFP within 4 h. Recovery of VICC occurred after a median of 14.4 (IQR: 11.5–17.5) h, and only the use of FFP within 4 h influenced the time to recovery. Neither antivenom dose nor time of antivenom administration had an effect on recovery of VICC. In patients administered with FFP, 12% [credible interval (CrI): 6–21%] and 81% (CrI: 61–94%) had recovered at 6 and 12 h, respectively, vs 2.5% (CrI: 1.5–4%) and 28% (CrI: 22–34%) not receiving FFP.

Discussion: Antivenom did not appear to be effective for the coagulopathy in snake envenoming in Australia. FFP appeared to shorten the time of VICC recovery.

Introduction

Snake envenoming is a major cause of injury in the rural tropics. A common manifestation of severe envenoming is venom-induced consumption coagulopathy (VICC).^{1–5} Antivenom is a mainstay of management although there have been no placebo controlled trials to confirm its effectiveness. In VICC, the aim of antivenom therapy is to bind circulating venom components that activate clotting

pathways, preventing further consumption and thereby promoting clotting function recovery. In Australia, the presence of VICC is used to initiate antivenom treatment in about three-quarters of all cases of snakebite receiving antivenom.⁴

We recently developed a semi-mechanistic systems model of the coagulation pathway and simulated the effects of taipan venom on the pathway.⁶ These simulations matched well with clotting factor data obtained from real taipan bites. They also

Address correspondence to G.K. Isbister, Calvary Mater Newcastle Hospital, Edith St, Waratah NSW 2298, Australia. email: geoffrey.isbister@menzies.edu.au

indicated that neutralization by antivenom must occur almost immediately after venom enters the circulation to significantly impact on recovery time of the coagulopathy.⁶ This has profound implications for antivenom therapy in VICC, at least that resulting from Australian snake bite. The model suggests that antivenom may not be effective in the treatment of the coagulopathy if given more than an hour after envenoming.

Unfortunately, it is difficult to test this hypothesis in envenomed patients. A placebo controlled trial of antivenom would be ethically challenging and logistically very difficult to conduct in Australia. A different approach is to investigate the effect of the timing of antivenom on the recovery of VICC. If antivenom is effective, then administration of antivenom within a reasonable period of time after the bite (i.e. <6 h) should significantly reduce the time to recovery of VICC and earlier administration times should have progressively greater effects on recovery. Our aim was to assess whether time to recovery of VICC is shortened by earlier administration of antivenom and/or the use of fresh frozen plasma (FFP).

Methods

We analysed a cohort of patients with VICC recruited to the Australian Snakebite Project (ASP), a multicentre prospective observational study of snake bite cases from tertiary and regional hospitals and associated poisons centres around Australia. The pre-defined aims of ASP are to determine the effectiveness and safety of antivenom, using serial clinical and laboratory features as well as measurement of venom and antivenom concentrations. Approval has been obtained from Human Research and Ethics Committees covering all institutions involved in the study.

Recruitment can occur at any Australian hospital, and cases are identified by local investigators, calls made to poison information centres, calls to clinical toxicologists and toxinologists and from notifications by laboratory services. Demographics, clinical and laboratory details, first aid and treatment of patients are recorded on study datasheets and were made available to the treating hospital by fax from the chief investigators. Additional calls were made by the investigators to ensure that datasheets are faxed back to the investigators via a national fax number prior to discharge of the patient. Investigators and research nurses ensured that datasheets are completed and data are entered into a purpose-built relational database (Microsoft AccessTM). A few cases (<5%) were recruited shortly after the discharge from hospital, if the required data

can be verified from laboratory records, hospital notes and by communication with the treating doctors. Decisions about all treatments, including antivenom and factor replacement, were made by the treating doctor. Specific data collection protocols and datasheets for ASP have previously been published or are available from the authors.⁴ In Australia, antivenom is produced only by one manufacturer, CSL Ltd.

This cohort was enrolled between January 2002 and May 2008. Inclusion in this analysis required all of the following criteria:

- (i) definite or suspected snake bite;
- (ii) severe VICC defined as a coagulopathy [baseline/admission international normalized ratio (INR) >3 or a prothrombin time (PT) three times normal] and evidence of consumption (either an elevated D-dimer of at least 10 times normal or fibrinogen below the limit of quantification); and
- (iii) evidence of recovery in the form of either serial INR values with at least one value <2 or serial PT with one value <24 s. Patients who died prior to recovery of VICC were not included.

Information was extracted from the database on patient demographics, time of the bite, serial coagulation studies, type of snake based on snake venom detection kit or snake identification by a professional herpetologist, details of antivenom treatment (dose and time of administration) and factor replacement therapy (type and time of administration). Although the specific type of analysis and primary outcome in this analysis were not defined prior to the commencement of ASP, the objectives of ASP were to investigate the effectiveness of antivenom using pre-defined objective variables.

Analysis

The primary outcome was the time interval from bite to first INR <2 (or PT < 24 s) as a measure of progress to VICC resolution. This cut-off has been previously defined by the investigators in a laboratory study of VICC⁷ and was decided prior to any analysis being undertaken. A fully Bayesian survival analysis was developed in WinBUGS 1.4.3 to investigate the effect of predictor variables on the time to recovery of VICC. Predictor variables included—time interval from bite to antivenom, dose of antivenom, use of FFP within 4 h of first antivenom administration, age, sex and snake type (brown snake or tiger snake group).

The distribution of the time to recovery (event) was assumed to follow a Weibull distribution which allows for a non-constant hazard. Patients naturally recover from VICC and in our dataset all

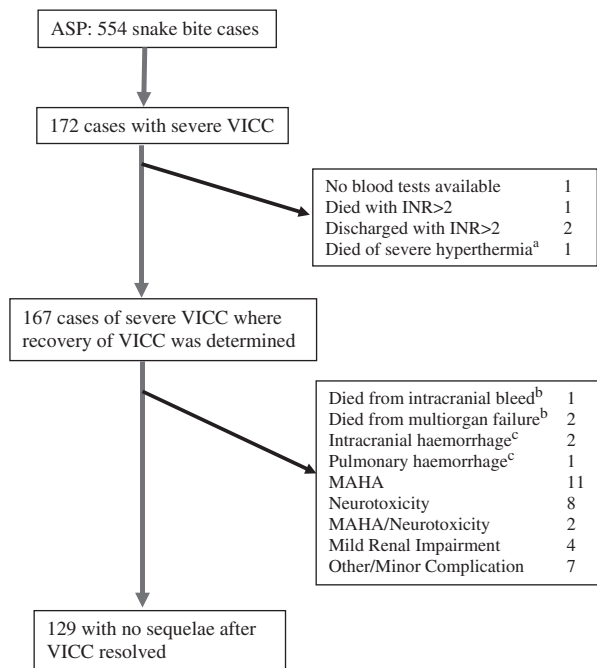


Figure 1. Flow chart showing the sample used in the study. ^aSuffered severe environmental hyperthermia after collapsing alone following a brown snake bite; ^bpre-hospital cardiac arrest (pre-antivenom); ^cbleeding complications present on admission pre-antivenom.

patients were followed until recovery. Predictor variables were included as covariates in the model. Model selection was based on deviance information criterion⁸ and decisions about the inclusion of covariates were made by examining the probability distribution of the coefficients. Goodness of fit of the model was investigated by comparing Kaplan–Meier plots to the predicted times to event from the model. To further explore, if antivenom decreases the time to recovery we dichotomized the time to antivenom based on administration before and after 6 h from the bite and excluded the patients receiving FFP.

Results

There were 167 cases of severe VICC with a median age of 41 [interquartile range (IQR): 28–53] years and 130 (78%) were males. One hundred cases were bites by brown snakes (*Pseudonaja* spp.), 60 were bites by tiger snake or related genera (*Notechis* spp., *Tropidechis* spp. and *Hoplocephalus* spp.) and seven were bites by taipans (*Oxyranus scutellatus*). Monovalent or polyvalent antivenom was administered in all cases at a median of 3.6 (IQR: 2.2–5.6; range 0.58–18) h after the bite and the median dose was four (IQR: 2–6 vials; range 0.2–17) vials. Twenty patients received FFP but only 13 patients

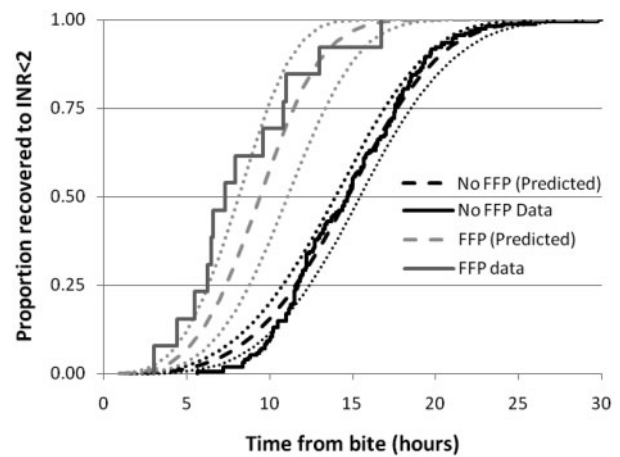


Figure 2. Predicted proportion (median, 2.5 and 97.5% CrIs) of patients recovered from VICC with (dashed grey) and without (dashed black) the administration of FFP within 4 h compared with Kaplan–Meier plots of the observed times of recovery of VICC for patients receiving (thick grey) and not receiving (thick black) FFP.

received FFP within 4 h of first antivenom administration. Three patients died after their coagulopathy resolved, and one patient was excluded who died prior to the coagulopathy recovering. All three patients who died presented to hospital following an early pre-hospital cardiac arrest within 1 h of the bite and at least a 10-min period without cardiopulmonary resuscitation and died of either hypoxic brain injuries or intracranial haemorrhage (Figure 1).

Recovery of VICC occurred at a median of 14.4 (IQR: 11.5–17.5; range: 3–29.8) h after the bite. Visual inspection of covariate plots for the time to recovery suggested a relationship between FFP and time to recovery (Figure A1). A time to recovery model provided a good fit to the data (Figure A2) and the only predictor variable that was significant was the administration of FFP within 4 h of antivenom. The dose of antivenom and the time to antivenom did not reduce the time to recovery from VICC. In patients administered with FFP within 4 h of antivenom, 12% [credible interval (CrI): 6–21%] and 81% (CrI: 61–94%) had recovered at 6 and 12 h, respectively, vs 2.5% (CrI: 1.5–4%) and 28% (CrI: 22–34%) when FFP was not given (Figure 2). The significance of the effect of FFP was not influenced when adjusted for the other four factors.

One hundred and twelve of the 141 patients who did not get FFP received antivenom within 6 h of the bite—early antivenom group. In patients receiving early antivenom, 3% (CrI: 2–5%) and 33% (CrI: 26–39%) had recovered at 6 and 12 h, respectively, which was not different from the 3% (CrI: 1–4%) and 27% (CrI: 19–35%) recovery rates at 6 and 12 h, respectively, for antivenom given after 6 h (Figure 3).

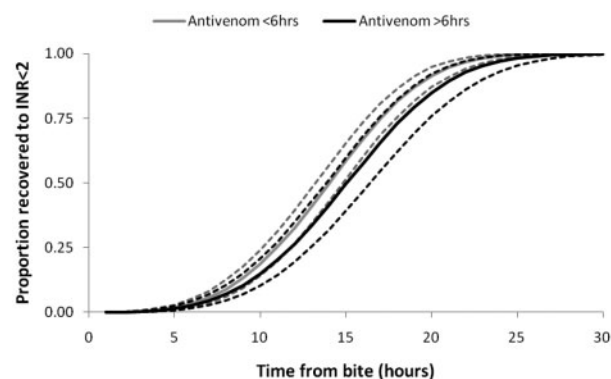


Figure 3. Predicted proportion (median—solid line; 2.5 and 97.5% CIs—dashed lines) of patients receiving antivenom within 6 h of the bite (early antivenom; black) vs patients receiving antivenom > 6 h after the bite (late antivenom; gray).

Discussion

In this study, neither earlier administration of antivenom nor higher doses of antivenom reduced time to recovery of VICC supporting predictions from a systems model of the coagulation pathway. However, early administration of FFP was associated with faster recovery. The estimation of the positive effect of FFP was highly precise with tight CIs. The effect of antivenom when administered before and after 6 h had tight CIs which overlapped. The latter indicates that antivenom appears ineffective to treat VICC.

There is an urgent shortage of antivenom in the rural tropics where snake envenoming is a major public health issue, and action is required to develop antivenoms for these regions.^{9,10} However, there must be proper evaluation of antivenoms as they are developed to ensure that they are effective. It is essential to evaluate the effectiveness of antivenom against specific effects, so that antivenom is only used where it will be beneficial. It has always been believed that antivenom therapy is effective in improving the recovery of coagulopathy in snake bite. For Australian elapids, this is now in doubt, and it is important that similar assessment is made for snake envenoming in other parts of the world.

The use of factor replacement in VICC remains controversial, and there are few studies investigating this issue.^{1,11,12} FFP is the most widely available factor replacement and its administration is aimed to rapidly replace important clotting factors including fibrinogen, factors V and VIII. However, there have always been concerns that factor replacement may ‘fuel the fire’ of the consumptive process. Evidence from this prospective study does not

support the ‘fuel on the fire’ conjecture in VICC caused by Australian elapids and indeed supports that FFP replacement greatly reduces the time to recover and potentially the risk of bleeding. This is consistent with a preliminary retrospective study from western Australia (prior to 2003) when FFP was commonly used to treat VICC.¹³ Randomized controlled trials of factor replacement must now be undertaken in snakebite coagulopathy.

Clearly, there are limitations in the design of this study because there was no placebo antivenom group, a limitation caused by its wide acceptance in current practice, and FFP administration was not randomized. However, the investigators were rarely involved in decision about the timing of antivenom, the use of FFP and this cohort study, therefore provides a source for this information and outcomes.

Conclusion

Current practice in the treatment of snakebite in Australia is far from optimal. Large doses of antivenom have become a part of normal practice,^{4,14} with little reference to whether further antivenom is likely to be beneficial. This exposes patients to large amounts of equine protein at a significant cost in the absence of strong evidence of effectiveness. Anaphylaxis is a substantial risk of antivenom treatment,^{4,15} and treatment with adrenaline in the context of coagulopathy introduces additional risks for lethal intracerebral haemorrhage. This study suggests that antivenom as it is currently used in Australia for VICC is ineffective. However, antivenom is still required in appropriately determined doses¹⁴ because other clinical effects such as neurotoxicity and myotoxicity are likely to be prevented or curtailed by early antivenom administration.

Acknowledgements

On behalf of the ASP clinical investigators who recruited patients to the study the authors would like to thank: 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), Nicholas Buckley (Canberra Hospital), Alan Tinkel (Coffs Harbour Base Hospital), Randall Greenberg (Dubbo Base Hospital), Mark Webb (Flinders Medical Centre), 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), Dan Connor (Manning Base Hospital), Peter Garrett, Mark Coghlan and David Ward (Nambour Hospital), Andrew Parkin and Colin Page (Princess Alexandra Hospital), Paul Davies (Rockhampton Hospital), Rod Ellis (Rockingham Hospital), Bart Currie (Royal Darwin Hospital), Ken Winkel (Royal Melbourne Hospital), Justin Yeung, David McCoubrie and Frank Daly (Royal Perth Hospital), Lindsay Murray 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 and Robert Dowsett (Westmead Hospital), Julian White (Royal Adelaide Hospital); and the ASP laboratory investigators including Margaret O'Leary, Jennifer Schneider, Sarah Just, Tony Ghent and Vaughan Williams. We also acknowledge the many referrals from the poison information centres and clinical toxicologists and help of the many other nurses, doctors and laboratory staff in recruiting patients and collecting samples.

Funding

The study was supported in part by NHMRC Project Grant 490305. G.K.I. is supported by an NHMRC Clinical Career Development Award ID300785 and S.G.A.B. is supported by NHMRC Career Development Award ID 513901.

Conflicts of interest: None declared.

References

- Warrell DA, Davidson NM, Greenwood BM, Ormerod LD, Pope HM, Watkins BJ, *et al.* Poisoning by bites of the saw-scaled or carpet viper (*Echis carinatus*) in Nigeria. *Q J Med* 1977; **46**:33–62.
- Lalloo DG, Trevett AJ, Owens D, Minei J, Naraqi S, Saweri A, *et al.* Coagulopathy following bites by the Papuan taipan (*Oxyuranus scutellatus canni*). *Blood Coagul Fibrinolysis* 1995; **6**:65–72.
- Milani RJ, Jorge MT, Ferraz dCF, Martins FP, Bousso A, Cardoso JLC, *et al.* Snake bites by the jararacucu (*Bothrops jararacussu*): clinicopathological studies of 29 proven cases in Sao Paulo State, Brazil. *QJM* 1997; **90**:323–34.
- Isbister GK, Brown SG, MacDonald E, White J, Currie BJ. Current use of Australian snake antivenoms and frequency of immediate-type hypersensitivity reactions and anaphylaxis. *Med J Aust* 2008; **188**:473–6.
- Mahasandana S, Rungruxsirivorn Y, Chantarangkul V. Clinical manifestations of bleeding following Russell's viper and Green pit viper bites in adults. *Southeast Asian J Trop Med Public Health* 1980; **11**:285–93.
- Tanos PP, Isbister GK, Laloo DG, Kirkpatrick CM, Duffull SB. A model for venom-induced consumptive coagulopathy in snake bite. *Toxicon* 2008; **52**:769–80.
- Isbister GK, Williams V, Brown SG, White J, Currie BJ. Clinically applicable laboratory end-points for treating snakebite coagulopathy. *Pathology* 2006; **38**:568–72.
- Spiegelhalter DJ, Best NG, Carlin BR, van der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Series B Stat Methodol* 2002; **64**:583–616.
- Theakston RDG, Warrell DA. Crisis in snake antivenom supply for Africa. *Lancet* 2000; **356**:2104.
- Laing GD, Harrison RA, Theakston RDG, Renjifo JM, Nasidi A, Gutierrez JM, *et al.* Polyspecific snake antivenom may help in antivenom crisis. *Br Med J* 2003; **326**:447–8.
- White J. Snake venoms and coagulopathy. *Toxicon* 2005; **45**:951–67.
- Porath A, Gilon D, Schulchynska-Castel H, Shalev O, Keynan A, Benbassat J. Risk indicators after envenomation in humans by *Echis coloratus* (mid-east saw scaled viper). *Toxicon* 1992; **30**:25–32.
- Brown SG, Caruso N, Borland ML, McCoubrie DL, Celenza A, Isbister GK. Clotting factor replacement and recovery from snake venom-induced consumptive coagulopathy. *Intensive Care Med* 2009, Jun 23. [epub ahead of print].
- Isbister GK, O'Leary MA, Schneider JJ, Brown SG, Currie BJ. Efficacy of antivenom against the procoagulant effect of Australian brown snake (*Pseudonaja* sp.) venom: in vivo and in vitro studies. *Toxicon* 2007; **49**:57–67.
- Premawardhena AP, de Silva CE, Fonseka MMD, Gunatilake SB, de Silva HJ. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *Br Med J* 1999; **318**:1041–3.

Appendix

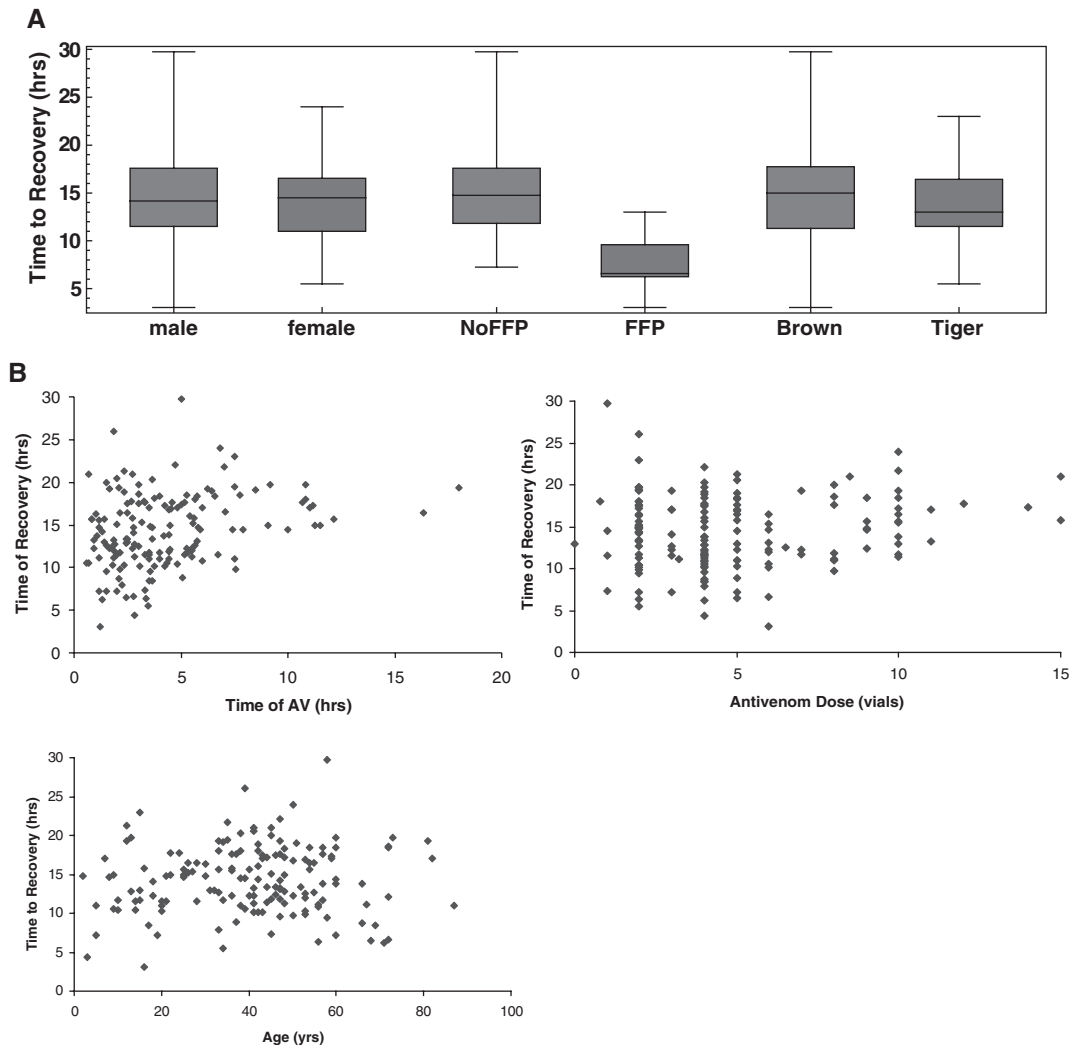


Figure A1. Comparison of time to recovery after the bite (not antivenom) for dichotomous covariates (A) and continuous covariates (B).

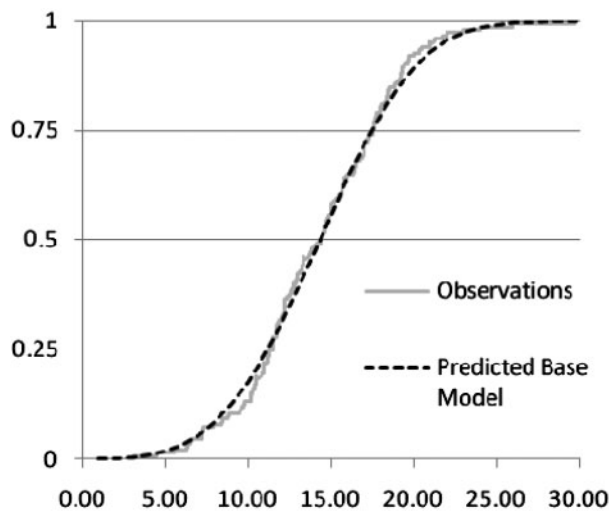


Figure A2. Comparison of the predicted mean proportion of patients recovering from VICC to a Kaplan–Meier plot of the patient’s data.