BMJ Case Reports

TITLE OF CASE

The Use of Rotational Thromboelastometry to Guide Management Following Bitis nasicornis Envenoming

SUMMARY

A man in his thirties presented following *Bitis nasicornis* envenoming. His coagulation was assessed using rotational thromboelastometry. It identified a subtle abnormality, not detected using standard laboratory assessments of coagulation, and influenced ongoing management. The abnormality resolved following treatment with antivenom. There are few documented cases of using rotational thromboelastometry to assess patients following haemotoxic envenoming. This case highlights some of the potential benefits and limitations of doing so.

BACKGROUND

The *Bitis nasicornis* (rhinoceros viper) is a venomous snake native to sub-Saharan Africa(1). Venomous snakes such as the rhinoceros viper are kept in the UK as domestic pets, both legally and illegally, and in zoos and research institutes. Only a small number of cases of human envenoming and their effects have been published(2,3).

The venom of *B. nasicornis* contains toxins from nine different families(4). It is primarily cytotoxic and haemotoxic, causing significant local tissue damage and coagulopathy, but also has neurotoxic and cardiotoxic effects demonstrated *in vitro*(5–8) and in animal studies(9). Documented human cases of *B. nasicornis* envenoming are rare, but one patient in Hungary developed significant swelling and prolongation of the International Normalised Ratio (INR 1.7) without active bleeding(2).

Rotational thromboelastometry (ROTEM) is a method for real-time viscoelastic testing of whole blood allowing assessment of clot formation, stabilisation, and fibrinolysis. ROTEM is currently used in several centres across the UK to guide transfusion in trauma, cardiothoracic surgery, obstetrics and major haemorrhage(10). The benefits over standard laboratory assessments of coagulation, including INR, activated Partial Thromboplastin Time (aPTT) and Fibrinogen, include the ability to assess all phases of coagulation and the speed at which the results are available. There are several documented cases of using ROTEM or thromboelastography (TEG) to assess coagulopathy in snake bites(11–16) but none specifically involving *B. nasicornis*.

CASE PRESENTATION

A man in his thirties with no past medical history was bitten by a legally imported *B. nasicornis* on the right index finger whilst working in a reptile store. As shown in Figures 1 and 2, there was a puncture

wound of the dorsal aspect of the proximal inter-phalangeal joint. The man presented to the Emergency Department (ED) approximately 30 minutes later with localised erythema and swelling. There was no evidence of active bleeding, his ECG was normal, and observations were stable, showing a National Early Warning Score 2 (NEWS2) score of 0. Initial bloods were taken including a venous lactate (1.6 mmol/L) and intravenous flucloxacillin and gentamicin was given based on the advice from the plastic surgery consultant. The case was discussed with the National Poisons Service with advice received from the Liverpool School of Tropical Medicine (LSTM). Over the course of five hours in the ED, the swelling worsened and began to affect the proximal arm, and venous lactate rose to 7.8 mmol/L prompting a fluid bolus and further discussion with LSTM. Seven hours after the bite the patient was given a tetanus booster, three vials of EchiTab plus-ICP antivenom (Instituto Clodomiro Picado, San Jose, Costa Rica) were administered and the patient was transferred to the Intensive Care Unit (ICU) for observation. Due to the potential risk of developing a coagulopathy, the patient was monitored with frequent standard laboratory assessments of coagulation, shown in Table 1, and ROTEM was used to further guide management. The ROTEM on admission to ICU, at 9 hours post envenoming (Figure 3), showed abnormalities, with a subtly prolonged clot formation time (CFT), reduced α angle and reduced maximum clot firmness (MCF) using extrinsic rotational thromboelastometry (EXTEM) and a mildly reduced MCF on fibrin-based rotational thromboelastometry (FIBTEM). This suggested deficiencies in the patient's clotting factors, particularly fibrinogen but no hyperfibrinolysis. None of the standard laboratory assessments of coagulation were abnormal during the patient's time on ICU.

Table 1: Laboratory results
Abbreviations: INR, International normalised ratio. aPTT, activated Partial Thromboplastin Time

Time since envenomation	1 hr	9 hrs	17 hrs	23 hrs	36 hrs	81 hrs	93 hrs	Normal range
Haemoglobin (g/L)	130	135	134	141	132	125	117	130 - 170
Haematocrit (L/L)	0.40	0.41	0.40	0.40	0.39	0.38	0.36	0.40 - 0.52
Platelets (10^9/L)	199	211	205	201	211	203	180	150 - 400
INR	1.1	1.2	1.2	1.1	1.0	0.9	1.0	
aPTT (s)	27.6	27.7	27.1	25.8	24.6	22.9	24.4	21.0 - 33.0
Fibrinogen (g/L)	2.3	2.1	1.9	2.6	3.1	3.2	2.9	1.5 - 4.0

The following day the swelling had again increased, now extending to affect the whole right arm, shoulder, and local areas on the back (Figure 2). ROTEM was repeated 17 hours after the bite (Figure 3) which continued to show a subtly abnormal MCF on FIBTEM suggesting ongoing issues with fibrinogen production or function. These two factors prompted further discussion with LSTM and the administration of three more vials of antivenom. Following this the ROTEM was repeated at 23 hours and 36 hours (Figure 3) which showed no further abnormality. No further antivenom was given and the patient was not treated with any blood products during their admission. During the first 36 hours the patient was

reviewed regularly by the plastic surgery team who clinically observed for evidence of compartment syndrome. A timeline of the patient's first 36 hours is shown in Figure 4.

INVESTIGATIONS *If relevant*

n/a

DIFFERENTIAL DIAGNOSIS *If relevant*

n/a

TREATMENT *If relevant*

n/a

OUTCOME AND FOLLOW-UP

The patient's swelling gradually improved. He was transferred to the ward after 2 days in ICU. He was discharged home after 5 days. The patient was seen in the plastic surgery clinic approximately two weeks later and had no swelling, ulceration or necrosis and had full use of his hand.

DISCUSSION

This case highlights the risk of non-native snake bites in the UK. The management of snake bite envenoming typically involves immobilisation of the bitten limb, close observation for complications, and laboratory evaluation including a full blood count, creatine kinase, renal function tests, INR, aPTT and a fibrinogen (or 20-minute whole blood clotting test (20WBCT) if coagulation tests are not available). Indications for antivenom are shown in Table 2. Torniquets are not recommended and complications such as compartment syndrome and cellulitis are rare(17–19).

Table 2: Indication for antivenom. Based on the WHO guidelines(19).
Abbreviations: 20WBCT, 20-minute whole blood clotting test, INR, International normalised ratio

Indications for antivenom
Haemostatic abnormalities: spontaneous systemic bleeding or abnormal clotting tests - Failure to clot during a 20WBCT, INR >1.2 or platelets <100x10^9/L
Neurotoxic signs: ptosis, opthalmoplegia, paralysis
Acute Kidney Injury: oliguria/anuria or raising blood creatinine / urea
Intravascular haemolysis: evidenced by haemoglobinuria and myoglobinuria Rhabdomyolysis: based on clinical signs or myoglobinuria
Significant local swelling: - involving more than half the bitten limb within 48 hours - rapid extension of swelling within a few hours - an enlarged tender lymph node corresponding to the bitten limb

This case demonstrates that ROTEM can be more sensitive to abnormalities in coagulation following snakebite envenoming than standard laboratory assessments of coagulation including INR, aPTT and fibrinogen(12,15,20). Hadley et al. found that TEG combined with the INR was a more accurate predictor of clinical outcome than INR alone(11) and Gooneratne et al. found ROTEM, in particular EXTEM-CT, was a better predictor of envenoming and the need for antivenom than 20WBCT(16). In some documented cases ROTEM or TEG detected an abnormality earlier that standard laboratory assessments of coagulation(12,13) or remained abnormal for longer(14). However, these cases described cover multiple species of snake and may not be generalizable.

The subtle abnormalities present on the two initial ROTEM samples, that of a reduced MCF using the FIBTEM assay, are generally caused by a problem with fibrinogen (either reduced production or impaired function). *B. nasicornis* venom is known to contain metalloproteinases that degrade fibrinogen by cleaving the α- and β- chains(21) which may be responsible for this abnormality, however the fibrinogen level in this patient were not significantly reduced. *In vitro* the venom *also* appears to inhibit the production of thrombin and reduces the production and increases the breakdown of thromboplastin(5) resulting in an anticoagulant effect not clearly demonstrated in this case. The venom of the closely related *B. gabonica* (Gaboon viper) has been more thoroughly studied. Following envenoming, patients have developed laboratory evidence of a coagulopathy(22) including a fall in fibrinogen and raised prothrombin time (PT) and can develop haemorrhage(23). Its venom has been shown to contain anticoagulant factors as well as procoagulant factors that can lead to a venom-induced consumption coagulopathy(24,25). More work is needed to understand the exact actions and mechanisms of *B. nasicornis* venom.

In this case, the combination of the abnormal ROTEM together with worsening arm swelling led to the decision to administer further antivenom. The patient had no evidence of haemorrhage and although the subtle abnormalities detected in the ROTEM analysis resolved following the second dose of antivenom, it is difficult to be sure whether ROTEM abnormalities alone would have justified further administration of antivenom. It is also not possible to determine whether the positive outcome in this case, resolution of the ROTEM abnormality or lack of any significant derangement of the standard laboratory assessments of coagulation was a result of the administration of a second dose of antivenom. ROTEM can undoubtedly detect more subtle signs of deranged coagulation than standard laboratory assessments of coagulation and may enable more rapid and frequent assessment of coagulation disturbance (if available). However, the clinical significance of such findings in not yet clear and the risk of antivenom administration should not be forgotten; Tambwe et al. utilised an abnormal ROTEM to guide repeat antivenom administration for one patient despite normal standard coagulation tests which resulting in a significant reaction(26). Severe reactions may occur with many antivenoms, depending upon the manufacturer(19).

ROTEM use in snake bites does have several limitations. Snake bites most often occur in areas where viscoelastic testing is not readily available. At present, ROTEM in snakebite has limited evidence for its utility over standard laboratory assessments of coagulation and the correlation between results is still unclear(27). Finally, snake venom components such as haemorrhagins can directly damage vascular tissue and cause haemorrhage; ROTEM would fail to detect this.

Overall, the authors believe ROTEM may be a useful additional tool to assess coagulopathy following snake bite envenoming. However, more work is needed to investigate whether it improves treatment of coagulopathy and has a beneficial effect on patient outcomes.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- Non-native snake bites can and do occur in the United Kingdom.
- ROTEM should be considered to help evaluate patients with envenoming known to affect coagulation.
- There is limited evidence of the value of ROTEM in assessing snake bites and further work is needed.

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FIGURE/VIDEO CAPTIONS

Figure 1: Envenomation site and arm swelling. Photograph taken approximately 3 hours post envenoming.

Figure 2: Envenomation site and increasing arm swelling. Photograph taken approximately 18 hours post envenoming.

Figure 3: ROTEM traces and values Abbreviations: ROTEM, rotational thromboelastometry; A5, clot firmness (in mm) at 5 minutes; A10, clot firmness (in mm) at 10 minutes; MCF, maximum clot firmness; CT, clotting time; CFT, clot information time; IQR, interquartile range; INTEM, intrinsic rotational thromboelastometry; EXTEM, extrinsic rotational thromboelastometry; FIBTEM, fibrin-based rotational thromboelastometry.

Figure 4: Timeline following envenomation. Abbreviations: ED, Emergency Department; IV Ab, intravenous antibiotics; ICU, Intensive Care Unit; ROTEM, rotational thromboelastometry.

PATIENT'S PERSPECTIVE

n/a

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