

The role of thromboelastography in the management of children with snake-bite in southern Africa

G. P. Hadley¹, P. McGarr¹ and M. Mars² Departments of ¹Paediatric Surgery and ²Physiology, University of Natal, Durban, South Africa

Abstract

In the absence of a direct laboratory test of envenomation, there is a need for an alternative mechanism for the early recognition of envenomation following snake-bite in children. A severe clinical diathesis may result either from envenomation or from the release of an inappropriate tourniquet applied as 'first-aid' often several hours before presentation to hospital. Abnormalities of clotting are associated with both events. A normal thromboelastogram (TEG) provides early recognition of patients in whom the clinical course is likely to be benign (sensitivity = 94%). An abnormal TEG identifies patients of whom 50% will develop a severe clinical diathesis. A TEG is a more accurate predictor of disease severity than International Normalized Ratio alone. The TEG does not supplant clinical observation in the management of snake-bite in children but allows stratification into high- and low-risk categories.

Keywords: snake-bite, envenomation, children, prognosis, thromboelastography, South Africa

Introduction

Snake-bite in children is common throughout the tropics and subtropics. The small mass of a child reduces the volume of distribution, and therefore increases the likelihood of clinically significant toxicity of a given dose of venom. All snake-bites cause alarm but it is sometimes forgotten that not all snakes are venomous and that not all attacks by venomous snakes result in envenomation of the victim (TIBBALS, 1992). The situation is compounded for the clinician by the fact that the exact circumstances of injury are often unclear and evidence of fang marks may be obscured by scarification performed by a traditional healer, or by oedema. Further, tourniquet application is still regarded as appropriate first-aid in many communities and identification of the snake is rare (MARS *et al.*, 1991; YERZINGATSIAN, 1997). This situation pertains throughout much of sub-Saharan Africa, yet the potential toxicity, scarcity and cost of antivenoms make it desirable that envenomation be precisely diagnosed.

Snake populations differ in different parts of the world and therefore patterns of envenomation will also differ. Tests of envenomation and venom detection kits based upon the species of snake prevalent in one area may not be relevant to any other area. No specific tests for envenomation by the snakes prevalent in southern Africa are currently available. Thus direct laboratory confirmation of envenomation is not possible and reliance must be placed on clinical observation and indirect indices such as clotting dysfunction.

Snake venoms are traditionally divided into cytotoxic, haemotoxic and neurotoxic groups depending upon their principal action. However, venoms are complex mixtures of active agents and few, if any, will have a single 'pure' effect (ISEMONGER, 1983). In addition, snake-bite provokes a tissue response with *inter alia* the release of vasoactive cytokines. Antivenom may restore some elements of the clotting process whilst having no effect on others, e.g., thrombocytopenia, suggesting that the latter may not be a direct venom effect (BOND & BURKHART, 1997) but a secondary response. Based on these observations we have postulated that any significant envenomation will have a measurable effect on the clotting process which, even though the effect is subdominant, will be detectable by a dynamic assessment such as a thromboelastogram (TEG). This postulate is not accepted by all opinion and some maintain that certain venoms, particularly neurotoxic venoms, have a single pure action. Resolution of the controversy must await the assessment

of coagulopathy using TEG in a series of patients following neurotoxic envenomation.

From a practical point of view an Australian series showed that all envenomated children demonstrated coagulopathy when assessed by prothrombin index (PI), partial thromboplastin time (PTT), fibrinogen levels and fibrinogen degradation products (FDP), independent of the species of snake (TIBBALS, 1992). No child in whom envenomation was not confirmed showed evidence of coagulopathy. The study concluded that coagulopathy is a highly sensitive, specific and reliable indicator of envenomation (TIBBALS, 1992) independent of the species of snake.

It has also been shown that the ischaemic reperfusion injury associated with prolonged tourniquet use results in disturbances of coagulation (PETAJA *et al.*, 1987). We have therefore looked at the TEG, as an indicator of envenomation and as a predictor of a severe disease diathesis.

The TEG is a dynamic mechanical study of the coagulation process from fibrin formation through platelet aggregation to fibrinolysis. Various relevant parameters including the time to initiation of clot formation (*r*-time), the rate of clot formation (*k*-time) and the strength of the resultant clot (*ma* or maximal amplitude) are measurable from the TEG tracing (Figure). The TEG has been extensively used in the management of clotting dysfunction in cardiac and transplantation surgery (KANG *et al.*, 1985, 1989), and has been shown to be a sensitive indicator of early sepsis in the neonate (GRANT & HADLEY, 1997). Both hyper- and hypocoagulability are significant and the precise TEG abnorm-

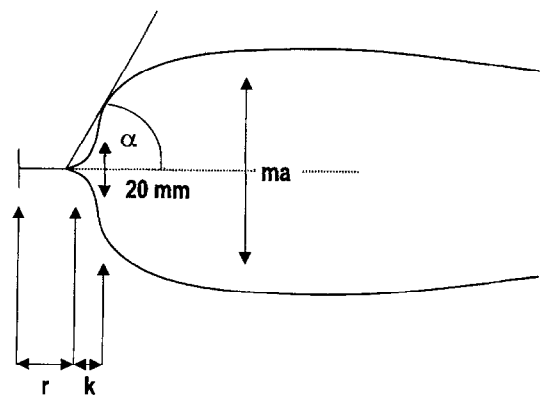


Figure. Normal thromboelastogram showing the time to initiation of clot formation (*r*-time), the rate of clot formation (*k*-time) and the strength of the resultant clot (*ma* or maximal amplitude).

ality is dependent upon the timing relative to the evolving pathology. The TEG has been used to monitor the coagulation deficit associated with bites by the specifically haemotoxic boomslang (AITCHISON, 1990), but has not been assessed as an index of envenomation or reperfusion injury.

Patients and Method

Over a 7-year period 1991 to 1997, 284 children with suspected snake-bites were admitted to King Edward VIII Hospital in Durban. In 96 of these patients a TEG was performed on admission, and of these 51 had TEG tracings available for review and were included in the study. The TEG, International Normalized Ratio (INR), length of hospital stay, use of tourniquet and clinical severity of the snake-bite were assessed.

Normal TEG parameters were defined as: r-time 6–8 min, k-time 3–6, ma 50–60 mm as described by MALLET & COX (1992). The INR was regarded as abnormal if it exceeded 1.2.

Patients were divided into 2 groups depending upon the severity of the clinical syndrome. Patients were placed in the 'mild' group if there was no swelling, or swelling localized to the bite area, with no constitutional symptoms or signs. The disease diathesis was considered 'severe' if the whole limb was swollen, the patient required fasciotomy, or if systemic symptoms and signs developed during observation. The use of polyvalent antivenom was restricted to patients with a 'severe' clinical picture in whom there was disease progression under observation. Clinical stratification was made on admission. The subsequent clinical course was monitored and compared to the prediction of the TEG.

Statistical analysis was performed using the χ^2 test with Yates' correction where appropriate.

Results

Thirty-five of 51 patients had abnormal TEGs, and in 16 the TEG was normal. Only 1 patient with normal TEG on admission developed a severe clinical diathesis and in this patient the TEG became abnormal within 24 h, whereas 17 of 35 patients with an abnormal TEG developed a severe clinical picture (Table 1). This difference is statistically significant ($P = 0.003$). There was no significant difference in clinical severity between those who had a normal INR ($n = 25$) and those with an abnormal INR ($n = 14$) ($P = 0.2$).

Patients with an abnormal TEG stayed in hospital for a mean of 5.6 days, and those with a normal TEG for a mean of 2.5 days. Information on tourniquet use was available in 44 patients, 18 of whom were known to have had a tourniquet applied. Fifteen of the 18 patients had an abnormal TEG, with 6 of these 15 patients classified

Table 1. The thromboelastogram and International Normalized Ratio relative to clinical findings after snake-bite

| | Mild | Severe |
|----------|------|--------|
| TEG | | |
| Abnormal | 18 | 17 |
| Normal | 15 | 1 |
| INR | | |
| Abnormal | 6 | 8 |
| Normal | 16 | 9 |

Abbreviations: TEG, thromboelastogram; INR, International Normalized Ratio.

as having a severe clinical course. Of the 26 patients on whom no tourniquet was used, a normal TEG (10 patients) was significantly associated with a mild clinical picture ($P = 0.037$).

When used to predict a severe clinical course the TEG had a sensitivity of 94% but a low specificity of 46%. The predictive value of a normal TEG for a mild clinical course was also 94%. The predictive value of an abnormal test was, however, low at 49% and the overall accuracy was 63% (Table 2).

INR status ($n = 49$) was not significantly different between clinical groups ($P = 0.2$), nor was the INR significantly different in the presence or absence of a tourniquet ($P = 0.25$). The predictive value of a normal INR was 64%, and of an abnormal INR 57%, with an overall accuracy of 62%. In combination, the predictive value of both tests normal was 86% and both tests abnormal 70%. The result of blood counts and PTT are summarized in Table 3.

Table 2. Sensitivity, specificity and predictive value of the thromboelastogram and the International Normalized Ratio based on an abnormal test result being associated with a serious outcome after snake-bite

| | TEG (%) | INR (%) | TEG + INR (%) |
|-----------------------------------|---------|---------|---------------|
| Sensitivity | 94.4 | 47.1 | 87.5 |
| Specificity | 45.5 | 72.7 | 66.7 |
| Predictive value of abnormal test | 48.5 | 57.1 | 70.0 |
| Predictive value of normal test | 93.8 | 64.0 | 85.7 |
| Accuracy | 62.7 | 61.5 | 76.5 |

Abbreviations: TEG, thromboelastogram; INR, International Normalized Ratio.

Table 3. Results of blood counts and partial thromboplastin time in relation to thromboelastogram result after snake-bite

| | Haemoglobin (g/dL) | White cell count ($\times 10^{-9}/L$) | Platelet count ($\times 10^{-9}/L$) | PTT (s) |
|--------------------|--------------------|---|---------------------------------------|-----------|
| TEG normal | | | | |
| Mean | 11.5 | 12.7 | 379.1 | 28.8 |
| Range | 8.8–14.5 | 6.1–19.9 | 249–828 | 23.2–35.1 |
| Median | 11.6 | 13.0 | 332 | 29.6 |
| Standard deviation | 1.4 | 4.1 | 148.4 | 12.0 |
| n | 14 | 13 | 13 | 12 |
| TEG abnormal | | | | |
| Mean | 11.6 | 13.6 | 338.4 | 33.2 |
| Range | 5.7–16.1 | 7.1–33.2 | 45–865 | 21–120 |
| Median | 12.0 | 12.1 | 323 | 28.4 |
| Standard deviation | 2.4 | 6.1 | 166 | 19.8 |
| n | 33 | 33 | 32 | 23 |

Abbreviations: TEG, thromboelastogram; PTT, partial thromboplastin time.

Discussion

The clinician presented with a child who has reportedly been bitten by a snake faces a dilemma. Knowing that there is the possibility that the child has not been envenomed, and that the clinical picture may be due to inappropriate interventions such as tourniquet application, he/she must decide whether the use of potentially dangerous therapy in the form of specific or polyvalent antisera is justified. Concern is heightened by the knowledge that the small mass of the child will increase the risk of significant envenomation.

Coagulopathy has been previously noted to be a reliable and specific indicator of envenomation in children (TIBBALS, 1992) suggesting a potentially useful role for the TEG in this difficult clinical dilemma. It is acknowledged that the TEG will identify abnormalities of the clotting process but not the cause of those abnormalities. In the context of snake-bite, the child with a normal TEG has a less severe clinical picture and a shorter hospital stay. It is predictable that an abnormal TEG would not differentiate between envenomation and reperfusion injury. Normality of the TEG would, however, be expected to identify those patients without either insult, and this it does. The TEG would therefore appear to be a useful predictor of the severity of the disease diathesis. Establishing normal values for clotting function measured by TEG in children is problematic. It is also recognized that care must be taken in the acquisition of blood specimens for study and in the technique of performing a TEG. This may also introduce a bias against the predictive value of the TEG.

Tourniquet use is itself an inconstant parameter as times of application and pressure differ between patients and these are unknown and immeasurable. There is no doubt that use of a tourniquet impacts negatively on the victim of snake-bite, probably through reperfusion injury, and contributes to the abnormal clotting profiles of these patients. The TEG remains a reliable predictor of the clinical course independent of tourniquet use.

INR is shown to be a poor indicator of clinical outcome. A normal TEG has better predictive value (94%) for a mild clinical course than a normal INR (64%). In contrast, both an abnormal TEG (49%) and an abnormal INR (57%) are relatively poor predictors of a severe outcome. The combination of TEG and INR improves the predictive value of an abnormal test to 70% and reduces the predictive power of a normal test to 88%.

In the absence of specific venom detection kits, tests of

coagulopathy are useful predictors of outcome. Of these, the TEG is more useful than INR alone. The TEG cannot replace clinical assessment of severity of injury in patients with snake-bite, nor the need for continuous reassessment, but we have found it a useful early warning signal. A normal TEG provides assurance that envenomation or reperfusion has not affected the clotting cascade and therefore the clinical syndrome is unlikely to be severe. Conversely, an abnormal TEG predicts a severe disease diathesis in 50% of patients and the possible need for more careful observation and more aggressive therapy.

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Received 12 June 1998; revised 12 January 1999; accepted for publication 12 January 1999

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