The Assessment and Treatment of Coagulopathy

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Introduction

Many snake venoms contain toxins which interfere with normal haemostasis and the targets of venom haemotoxins are as diverse as the enzymatic coagulation reactions themselves.

The role of haemostasis is to successfully maintain the integrity of the circulation by ensuring that the processes of clot formation and clot degradation remain in equilibrium at all times. Both of these pathways involve step-wise biochemical reactions that activate inactive blood clotting factors in an ordered sequence that leads to either the production of a viable blood clot at the site of a breach in the circulatory system such as a cut or scratch, or the breakdown and removal of that same clot once the underlying tissue has begun to heal.

Snake venoms that interfere with these sequential reaction pathways have the ability to seriously compromise the haemostatic integrity and to cause life-threatening haemorrhage.

An early coagulopathy is an absolute indication for the administration of antivenom in a patient suspected as having been bitten by a venomous snake in Papua New Guinea.

Coagulation disturbances have been documented following the bites of three common highly venomous snakes: Papuan taipans (*Oxyuranus scutellatus canni*), Papuan blacksnakes (*Pseudechis papuanus*) and small-eyed snakes (*Micropechis ikaheka*). They are also a prominent feature in bites by brown snakes (*Pseudonaja textilis*). Slight subclinical changes in haemostasis have been seen after bites by death adders (*Acanthophis* spp.), but these are not likely to be clinically significant.

In southern Papua New Guinea, where the Papuan taipan (*Oxyuranus scutellatus canni*) may be responsible for more than 80% of the serious snakebites, coagulopathy is common and may be severe. Venom from this snake converts prothrombin to thrombin in the presence of Ca^{2+} and circulating phospholipids in a Factor V-independent reaction. Systemic prothrombin activation causes depletion of available fibrinogen resulting in consumption coagulopathy and incoagulable blood. Disseminated intravascular coagulopathy results, and bleeding may occur from mucosal membranes, bite wounds, minor cuts or grazes, and venepuncture sites.

In the Milne Bay, Central, Gulf and Western provinces it is extremely likely that a person who presents with incoagulable blood has been bitten by a Papuan taipan (*Oxyuranus scutellatus canni*), and the early detection of this abnormality and recognition of its clinical significance is crucial to successfully treating bites by this extremely venomous snake.

This chapter briefly describes the major mechanisms of snake venom-induced coagulopathy, outlines the diagnosis and assessment of resultant haemostatic disturbances, and explains the process of clinical treatment and management.

Mechanisms of snake venom coagulation disturbances

The majority of coagulation disturbances observed in victims of snakebite in Papua New Guinea are due to either of the following:

Prothrombin activation

The conversion of the zymogen prothrombin to active thrombin enables soluble fibrinogen to be, in turn, converted into insoluble fibrin which provides the essential matrix for the formation of a viable blood clot at the site of an injury.

Prothrombin activation is tightly regulated, but may be seriously compromised by snake venoms procoagulant toxins, which are able to catalyse the cleavage of prothrombin to thrombin in the presence of phospholipid-rich platelets and circulating Ca^{2+} ions. Under normal conditions, this reaction is driven by Factor X_a, and another blood clotting enzyme (Factor V_a) is needed in order to optimise the reaction rate. However, some snakes, including the Papuan taipan (*Oxyuranus scutellatus canni*), have developed toxins that mimic both Factor X_a and Factor V_a, effectively substituting themselves for the natural factors.

Venom-induced activation of prothrombin results in uncontrolled, excessive thrombin production, leading to a disseminated intravascular coagulopathy (DIC) that involves:

- Systematic conversion of fibrinogen to fibrin.
- Activation of Factor XIII to Factor $XIII_a$, required for formation of cross-linked fibrin clots.
- Excessive consumption of fibrinogen, prothrombin, platelets and clotting factors.
- Activation of fibrinolysis by endothelial cell-secreted plasminogen activators.
- $Alpha_2$ antiplasmin consumption, leading to overabundant plasmin availability and the degradation of both fibrinogen and fibrin.
- Failure of haemostasis, with overwhelming defibrination, producing incoagulable blood and a pronounced bleeding diathesis.

Incoagulable blood (hypofibrinogenaemia) leads to bleeding from a variety of sites including:

- Gingival sulci,
- Gastrointestinal mucosa,
- Nasal mucosa,
- Venepuncture sites,
- Minor cuts, scratches or grazes including the bite site,
- Uterine membranes,
- Capillaries in the eyes, lungs, and brain.

It is important to note that consumption coagulopathy results in critical depletion of clotting factors, through their use as substrates and cofactors for venom-induced thrombin production. Also that, in the absence of venom neutralisation by antivenom, the replacement of these depleted clotting factors with FFP, cryoprecipitate or other blood products is very likely to promote further defibrination and hypofibrinogenaemia. Blood products **should not be used** until circulating venom has been neutralised with appropriate antivenom, except in cases of severe, immediately life-threatening haemorrhage.

Platelet function alteration

Platelets are small, disc-shaped, non-nucleated blood components that have phospholipid-rich plasma membranes that serve as the substrates for several important haemostatic processes, including the activation of prothrombin by both direct and indirect means.

Platelets are activated in response to haemostatic disruption, and will adhere and aggregate at injury sites where they act as temporary plugs, and stimulate coagulation factors in plasma to activate mechanisms in clotting pathways. Inhibitors of platelet aggregation can lead to true anticoagulation in which the normal pathways to prothrombin activation and fibrin clot formation are effectively disrupted, resulting in incoagulable blood.

There are inhibitors of platelet aggregation in the venoms of Papua New Guinea snakes that can produce anticoagulant effects (bleeding tendencies) without defibrination. From a clinical perspective, the haemostatic effects of these toxins are usually less severe than those produced by prothrombin activation. The venoms of the Papuan blacksnake (*Pseudechis papuanus*), small-eyed snake (*Micropechis ikaheka*) and death adders (*Acanthophis* spp.) have all been found to contain inhibitors of platelet aggregation.

Assessment and recognition of coagulopathy

Coagulation disturbances often develop rapidly after envenomation, and may be pronounced some time before the first symptoms or signs of neurotoxicity become apparent.

Recognising coagulopathy at the earliest possible time point can aid in the identification of the biting species and enable antivenom to be administered without delay. Coagulopathy in a person with suspected snakebite is an **absolute indication for antivenom**.

The 20WBCT (20 minute whole blood clotting test)

The 20WBCT (20 minute whole blood clotting test) should be performed on **ALL PATIENTS** with suspected snakebite in Papua New Guinea immediately after presentation at an aid post, health centre or hospital.

Equipment

- Latex gloves and 70% alcohol wipes.
- New, sterile needle and disposable syringe.
- Clean, dry glass bottle or sample vial.
- A watch or clock.

Procedure

1. Wearing gloves, swab the site carefully and perform venepuncture to collect 2 ml of fresh venous blood from an appropriate venepuncture site, such as the antecubital vein, of from the IV cannula, if you decide to insert one.
2. Carefully transfer the blood to the glass container and place the sample where it will not be disturbed and **do not touch it** for a minimum of 20 minutes.
3. Dispose of used sharps appropriately.
4. After 20 minutes, tilt the glass vial/bottle gently over onto its side and observe whether or not a functional clot has formed.
5. Record the result on the observation chart **clearly** as either ‘clotted at 20 minutes’ or ‘unclotted at 20 minutes’

Appearance of the blood at 20 minutes

- If the blood is incoagulable after 20 minutes, it will appear to have a 'watery' consistency and this is regarded as a **positive** test result.
- Clotted blood will 'clump' in the bottom of the glass vial as a 'jellylike' consistency and this is regarded as a **negative** test result.

Rationale and interpretation of the 20WBCT result

- If the blood is incoagulable after 20 minutes, the patient has a 98.4% chance of developing neurotoxicity if the bite is not treated with appropriate antivenom immediately.
- A patient with incoagulable blood after 20 minutes has hypofibrinogenaemia resulting from a consumption coagulopathy (DIC) and should receive appropriate antivenom as soon as possible.
- In Milne Bay, Central, Gulf and Western provinces, a **positive** 20WBCT strongly indicates a presumptive identification of envenomation by the Papuan taipan (*Oxyuranus scutellatus canni*), and either CSL taipan antivenom or CSL polyvalent antivenom should be administered.
- In other provinces a **positive** 20WBCT suggests either brown snake (*Pseudonaja cf. textilis*) or small-eyed snake (*Micropechis ikaheka*) envenomation, and CSL polyvalent antivenom should be administered.
- A **negative** test (clotting blood at 20 minutes) does not mean that a venomous snakebite has not occurred. The patient should continue to be observed hourly for a minimum of 24 hours and the 20WBCT should be repeated after six (6) hours.

Repetition of the test

- The 20WBCT can be used to assess the neutralization of circulating venom with antivenom, and should be **repeated six (6) hours** after the administration of antivenom.
- A positive 20WBCT (ie. the blood is not clotted after 20 minutes) six hours or more after antivenom administration indicates that circulating snake venom has not been fully neutralised and that more antivenom may be required.

Important considerations for proper use of the 20WBCT

- **Always** take appropriate precautions when drawing blood and handling blood, and take care with sharps to avoid needle-stick injury.
- **Use only clean dry glass tubes**: plastic tubes are not suitable and will not give a proper result. Do not use glass bottles washed with detergent, as their ability to activate clotting will be reduced.
- **Be patient**! Do not tilt or shake the tube during the 20 minute 'clotting interval': disturbing the sample will only delay clot formation and this can cause false-positive results that invalidate the test.
- **Do not** draw blood from the same limb in which an intravenous line has been established, unless you have first stopped the infusion for at least 10-15 minutes.
- **Take care** when drawing blood to minimise the risk of haematoma or bleeding from the venepuncture site afterwards.
- **Record** both the time the 20WBCT was carried out and the results of the test itself on the snakebite observation chart **each time** that it is performed on the patient.

Other tests of coagulation status

The following specific tests of coagulation status are typically only available in larger hospitals with functional pathology facilities:

1. Prothrombin Time (PT)

- Measures the function of clotting factors involved in the extrinsic and common pathway mechanisms of the coagulation cascade (i.e. Factors II, VII, X, fibrinogen and fibrin).
- Normal range for is 12-16 seconds.
- In patients with snake venom-induced DIC or anticoagulation, the PT will be prolonged, and can be greater than 150-180 seconds.

2. Activated Partial Thromboplastin Time (APTT)

- Measures the function of clotting factors involved in the intrinsic and common pathway mechanisms of the coagulation cascade (i.e. Factors X, XI, XII, XIII etc).
- Normal range is 25-47 seconds.
- In patients with snake venom-induced DIC or anticoagulation, the APTT will be prolonged, in some cases grossly so (i.e. >300 sec).

3. Fibrinogen Level

- Normal range is 1.5-4.5 g/L.
- In a patient with a DIC involving defibrination, the fibrinogen level will be critically below these ranges, and is often undetectable.
- Depletion of fibrinogen is not seen in bites by species with anticoagulant venoms.

4. Fibrin-degradation Products (FDP)

- Normal range is <10 µg/ml.
- In a patient with a DIC involving defibrination, the FDP may be extremely high.
- FDP levels are not typically elevated in bites by snakes with anticoagulant venoms.

5. Platelet Counts

- Normal range is 150-500 $\times 10^9$/L.
- A range of 50-100 $\times 10^9$/L indicates mild to moderate thrombocytopenia.
- < 50 $\times 10^9$/L suggests severe thrombocytopenia.

6. White Cells Counts

- Normal range is 4,000-11,000 $\times 10^6$/L.
- Following snakebites the WBC may be higher than 30,000 $\times 10^6$/L.

In a patient with a positive 20WBCT, a prolonged PT and APTT, with depleted fibrinogen and elevated FDP levels, confirms a disseminated intravascular coagulopathy involving defibrination, as would be seen after Papuan taipan (*Oxyuranus scutellatus canni*) envenomation.

In a patient with a positive 20WBCT, a prolonged PT and APTT, but normal fibrinogen and FDP levels, the coagulation disturbance is one of anticoagulation and probably due to a bite by either a Papuan blacksnake (*Pseudechis papuanus*) or a small-eyed snake (*Micropechis ikaheka*).

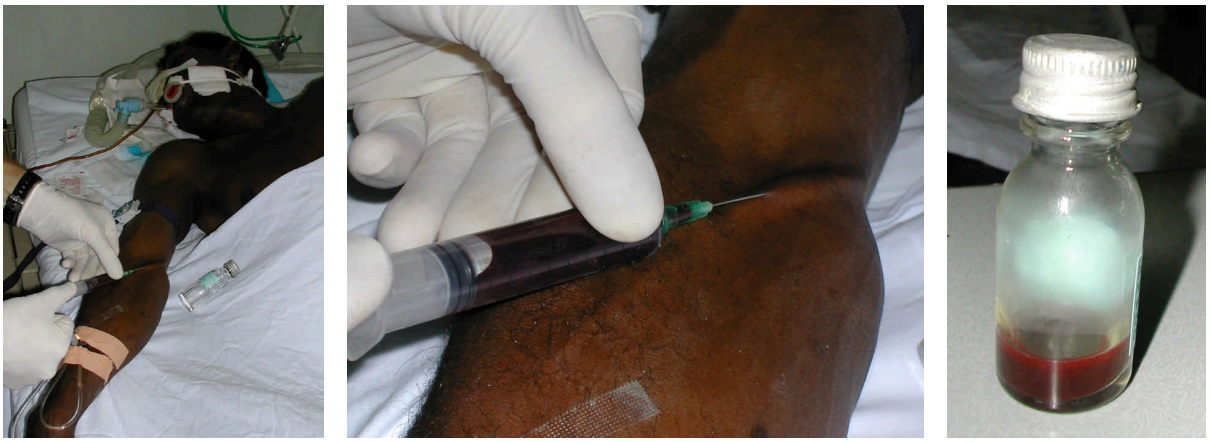

FIGURE 1: 20WBCT (20 minute whole blood clotting test) in a severely envenomed patient bitten by a Papuan taipan (*Oxyuranus scutellatus canni*). When drawing blood ensure that **(a)** gloves are worn, **(b)** precautions against needle-stick injury are taken (including proper sharps disposal), **(c)** a clean, dry glass container is available at the bedside, **(d)** venepuncture is performed with consideration to minimising subsequent bleeding or ecchymosis at the site, and **(e)** if drawing from the same limb that has been used for intravenous line access, turn off the IV for 10-15 minutes prior to the venepuncture to avoid contaminating or diluting the blood sample. Once drawn, place 2 ml of blood in the glass container and **allow it to stand undisturbed for 20 minutes** before determining the test outcome as either **(1)** 'clotted at 20 minutes' or **(2)** 'unclotted at 20 minutes'.

Symptoms and clinical signs of coagulation disturbances

The commonly reported **symptoms** of abnormal coagulation are:

- Unabated bleeding from the bite site,
- Bleeding from the sites of minor cuts, scratches or grazes, including those that can occur if the patient collapses and loses consciousness after the bite,
- Spitting or vomiting of blood,
- Bleeding from the gums and the nose.

Clinical **signs** of coagulopathy include:

- A positive 20WBCT (the blood is unclotted at 20 minutes),
- Bite site or venepuncture ecchymoses,
- Haematemesis,
- Haemoptysis,
- Epistaxis,
- Haematuria,
- Haemoglobinuria,
- Menorrhagia (at any age) or retroplacental bleeding (pregnant women),
- Retinal or subconjunctival haemorrhage,
- Bloody diarrhoea or per rectal bleeding or malaena,
- Prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT),
- Fibrinogenaemia and grossly elevated FDP levels,
- Thrombocytopenia,
- Intracranial bleeding (may appear like a stroke; leading to coma and death).

Monitoring of haemostasis in rural health centres

Rural health centres in Papua New Guinea do not generally have access to the resources of pathology clinics in urban centres, and cost means that even in urban hospitals many laboratory tests are either unavailable or uneconomical on the basis of cost.

The most important non-laboratory means of monitoring the haemostatic integrity of a patient with suspected envenomation in a rural aid post or health centre is to properly perform the 20WBCT to determine whether or not the blood of the patient is coagulable, both upon admission and over the time that the patient remains under care.

In a rural environment the 20WBCT, therefore, has two critical roles:

- **As a specific and absolute indication for administration of appropriate antivenom** in a patient suspected of having been bitten by a venomous snake;
- **As a simple, rapid and effective test** of the coagulation status of the patient.

An appropriate simple plan for the use of the 20WBCT in the management of snakebite would be to:

1. Perform a 20WBCT on all suspected snakebite patients immediately upon presentation.

2. If the 20WBCT is positive (blood is unclotted at 20 minutes):
   - Administer appropriate antivenom without delay.
   - Wait six (6) hours before repeating the 20WBCT to assess coagulability.
   - If the patient continues to demonstrate frank bleeding, more antivenom may be needed within 1-2 hours of the first ampoule (the 20WBCT can be repeated to confirm the presence of persistent coagulopathy).
   - If the 20WBCT is still positive after 6 hours, consider giving more of the appropriate antivenom.

3. If the 20WBCT is negative (blood is clotted at 20 minutes) and the bite occurred <2 hours previously:
   - Wait one (1) hour and repeat the 20WBCT.
   - Observe hourly for signs of envenomation over 24 hours and repeat the 20WBCT after a further six (6) hours.
   - If signs of envenomation develop, treat with the appropriate antivenom.

4. Repeat the 20WBCT every six (6) hours after any antivenom until the result of the test is negative, i.e.: the blood shows some clot formation at 20 minutes, and there is no evidence of bleeding.

In conjunction with using repeated 20WBCTs to assess whether or not the blood is clotting, and if antivenom has restored haemostasis, it is also important to:

- Maintain strict hourly observation and assessment of the patient in accordance with a treatment and nursing plan.
- Ensure that both the signs that are present, and the signs that are not present at each examination are recorded on the patient's observation and treatment chart, because this sequential process will tell you whether the patient is improving or deteriorating.

- Monitor blood pressure, heart rate, respiratory rate and depth (and peripheral oxygen saturations, if possible) hourly; temperature can be measured 4-hourly.
- Minimise the risk of bleeding and ecchymoses at venepuncture sites by considering the use of a second i.v. cannula (inserted in the opposite arm) to draw blood samples.
- Treat shock with IV fluid (normal saline, Hartmanns, or colloid).

Treatment Strategies

Disseminated intravascular coagulopathy (DIC), involving defibrination and consumption of clotting factors, is the most commonly encountered disturbance of haemostasis following snakebite in Papua New Guinea.

In Milne Bay, Central, Gulf and Western provinces, the most common cause of snakebite-related DIC with defibrination is the Papuan taipan (*Oxyuranus scutellatus canni*).

Reversal of coagulation disturbances with antivenom

The **first and most important step** in the treatment of coagulopathy after snakebite is the earliest possible administration of the most appropriate antivenom.

The selection and use of antivenom is discussed in detail in Chapter 11.

Antivenom is necessary in order to neutralise the toxins that catalyse the enzymatic reactions of the coagulation pathways that produce catastrophic thrombin overproduction, defibrination and clotting factor consumption. Until the toxins responsible for coagulopathy are neutralised, the patient remains at significant risk of haemorrhage.

Use of FFP and other blood products

Blood products such as fresh frozen plasma (FFP), cryoprecipitate and fresh whole blood **should not be used** to treat snake venom-induced blood loss **until after** coagulation is restored with the administration of appropriate antivenom.

Administration of FFP and other blood products to a patient with un-neutralised circulating snake venom toxins is potentially dangerous because:

- The addition of new clotting factors provides new substrates and cofactors for use in the uncontrolled overproduction of thrombin.
- It increases the degree of fibrinolysis and contributes to worsening of the coagulation defect rather than its repair.

The only circumstances under which FFP, or any other blood product, should be given are:

- ***After antivenom administration*** has been shown to have neutralised the circulating haemostatic toxins and where bleeding has stopped but circulating clotting factor levels are slow to rise back to normal levels, perhaps as a result of impaired liver function, or protein malnutrition.
- In cases that involve severe spontaneous bleeding where antivenom has already been given, but the immediate bleeding tendency is life threatening.

Remember: If you give FFP or other blood products to a patient who has not received enough antivenom to neutralise the circulating procoagulant toxins, you potentially contribute to a worsening of the coagulopathy rather than an improvement!