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Twenty-minute whole blood clotting test delays detection of coagulopathy in snakebite, use international normalised ratio

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Introduction

Snake bite is a neglected tropical disease primarily affecting poor rural communities [1]. Snakes are estimated to cause 421,000 to 1.8 million bites and up to 94,000 deaths yearly; most patients affected are from South and South East Asia, Sub-Saharan Africa, and Central and South America [1]. Snake envenoming can cause local tissue injury and necrosis, venom-induced consumption coagulopathy (VICC), neuromuscular paralysis, myotoxicity, and thrombotic microangiopathy with acute kidney injury [2]. It can also lead to long-term effects, including disability due to amputations, deformities, contracture formation and chronic ulceration, and delayed psychological effects [3]. Currently, antivenom is the only specific treatment for snake envenoming [4]. Antivenom can be administered once a clinical diagnosis of systemic envenoming has been reliably established [5].

Sri Lanka has one of the highest incidences of snakebite in the world. Community-based estimates suggest approximately 80,000 snake bites, 30,000 envenomings, and 460 snakebite deaths occur annually in Sri Lanka [1]. Eventhough Sri Lanka has over 100 species of snakes, only five are considered snakes of the highest medical importance: Russell's viper (*Daboia russelli*), cobra (*Naja naja*), the kraits (*Bungarus caeruleus*), saw-scaled viper (*Echis carinatus*) and Merrem's hump-nosed viper (*Hypnale hypnale*). Most envenomings are due to viper bites; 35-45% are due to hump-nosed vipers, and 30-40% to Russell's vipers [6].

Venom-induced consumption coagulopathy (VICC) and twenty-minute whole-blood clotting test (WBCT-20)

VICC is the most critical acute systemic effect of snakebite worldwide and in Sri Lanka. It results from consuming clotting factors due to the action of procoagulant toxins in snake venom. VICC is life-threatening due to the risk of bleeding, particularly in severe envenoming by Russell's vipers [7]. Russell's viper venom contains factor V and X activators.These act early in the coagulation pathway, resulting in positive and negative feedback loops, leading to indirect consumption of factors V and VIII, in addition to consumption of fibrinogen [8]. On the other hand, thrombin-like enzymes in

hump-nosed viper venoms consume fibrinogen rather than fully activating the clotting pathway [8], so it only causes a mild form of VICC [9].

Indian polyvalent antivenom accelerates recovery from VICC in Sri Lankan Russell's viper envenoming [10]. Although no commercial antivenom is currently available for envenoming by hump-nosed viper in Sri Lanka, it may be available in the future [11]. Early administration of antivenom is essential to treat envenoming, including VICC. Hence, the early diagnosis of VICC is vital.

The prothrombin time or international normalized ratio (PT/INR) is currently considered the gold-standard test for the diagnosis of VICC, with an INR > 1.5 indicating VICC and for administering antivenom [8]. In resource-poor settings, the WBCT-20 has been used for decades to diagnose and monitor VICC and to decide if antivenom should be given. The WBCT-20 has never been validated or standardized, and despite this, it has been incorporated into World Health Organization (WHO) guidelines on snakebite management. Recent studies and reviews have shown that these bedside clotting tests have poor sensitivity in many settings, including diagnosing VICC in viper bite in Sri Lanka [12,13]. Currently, in Sri Lanka, the WBCT-20 is recommended for diagnosing VICC and is widely used in snakebite management [14,15]. In some Sri Lankan hospitals, the capillary blood clotting test is used as an alternative bedside clotting test to assess VICC in snakebite, again with no validation [16].

The WBCT-20 test was adopted to detect VICC in snake envenoming in the mid-1970s. However, neither the test nor the observation time of 20 minutes was validated in any setting [13]. There was no standardization of the test, including the size of the tube used and the procedure of the test. An observational study involving 140 cases of definite Russell's viper bite patients in Sri Lanka found that the WBCT-20 had a sensitivity of 40% and specificity of 100%. The WBCT-20 in this study was done according to a protocol by the treating team but with no proper standardization [17]. A subsequent clinical study was conducted in the same setting on authenticated snakebites, with the WBCT-20 performed by trained research assistants using new, clean glass tubes with standard dimensions. This standardized approach improved the sensitivity of WBCT-20 to 82% while maintaining a specificity of 98% [15]. Notably, 77% of patients with VICC had a severe coagulopathy with an INR of more than five in this study.

WBCT-20 misses over half of the patients with coagulopathy in the Sri Lankan setting

In a more recent validation study in Sri Lanka, we assessed the performance of several different WBCTs in detecting VICC. We performed 15, 20, and 25 min whole blood clotting tests on admission and 5 and 10-minute capillary blood clotting tests (CBCT-5 and CBCT-10) in a cohort of patients who presented to the Teaching Hospital, Anuradhapura during a 1-year-period from 2020 to 2021 [18]. The WBCT was performed by trained medical and nursing graduates by placing 1 ml of venous blood in new 5 ml borosilicate glass tubes with a 10 mm internal diameter. The tubes were left undisturbed throughout the observation period of 15 to 25 min [17,18]. For the CBCT, a finger was pricked, and a 1 to 1.5 cm blood column was drawn up in a fresh capillary tube and then placed in a horizontal position. At the end of 5 min (CBCT-5) and 10 min (CBCT-10), the tube was turned to a vertical position to determine whether there was stagnation of blood. Blood was collected simultaneously for a PT/INR and plasma fibrinogen. VICC was defined as incomplete when INR>1.5 and complete VICC INR equal or more than three. VICC occurred in 58% of patients in this cohort.

We found none of the bedside tests had a sensitivity above 50% in detecting VICC. The WBCT-15 had the best sensitivity of 47% for detecting incomplete VICC and 68% for complete VICC. The sensitivity of the WBCT-20, WBCT-25, CBCT-5 and CBCT-10 were worse. All tests detected complete and late VICC presenting two hours later and VICC due to Russell's viper bites. Hence, mild or incomplete VICC was missed in patients presenting early to the hospital using WBCT or CBCT.

Why has WBCT-20 failed in the Sri Lankan setting?

Our recent study showed that the WBCT-20 is better in detecting late patients because they tend to have more severe VICC at presentation. Therefore, the WBCT-20 may have performed well as a screening test in the past, in which most patients arrived late. Over the last 40 years, the time gap from bite to hospital admission in Sri Lanka has decreased [19], and over 75% of snakebite patients present to the first contact hospital within two hours of the bite, even in rural Sri Lanka [20]. In most patients at hospital admission, VICC is still not fully developed. Hence, the WBCT-20 is likely to be falsely negative. The WBCT-20 is expected to be positive in these patients if the test is repeated after two hours when the VICC has become more severe or complete. This means that although snakebite victims present to hospitals early, they have to wait longer to receive antivenom due to the dependence on WBCT-20 and the lack of reliable diagnostic tests that can detect VICC early [20]. Therefore, the WBCT-20 delays the diagnosis of VICC and hence delays antivenom in Sri Lankans [17,18].

INR should be used to detect and monitor VICC whenever available

Although an INR is not freely available, particularly in peripheral hospitals, and is expensive and resource-intensive compared to the simple and affordable bedside clotting tests, many hospitals (particularly the base and

provincial hospitals) have laboratory facilities for INR. We believe this additional cost of INR to the health system outweighs the benefits of the patient receiving antivenom early, preventing life-threatening complications such as significant bleeding and acute kidney injury, which are much more costly to manage.

We suggest the following amendments to the snakebite management guidelines and practices in Sri Lanka:

1. In diagnosing and monitoring VICC (envenoming), INR is preferred over bedside clotting tests, including WBCT-20. VICC is diagnosed when the INR exceeds 1.5 (VICC = INR >1.5).
2. When the INR is unavailable, and the WBCT-20 or any other bedside clotting test is negative, it should be repeated after 3 hours to exclude VICC.

Authors contributions

AS, SS, GKI conceived the idea; SW drafted the manuscript which was critically revised by AS, GKI and SS; all authors approved the final version of the manuscript.

Competing interests

None.

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