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Efficacy of intravenous hydrocortisone administered 2–4 h prior to antivenom as prophylaxis against adverse drug reactions to snake antivenom in Sri Lanka: An open labelled randomized controlled trial

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ABSTRACT

The prevention of adverse drug reactions to antivenom serum poses a formidable challenge in the management of snakebite. Hydrocortisone is being used concurrently with antivenom in order to prevent these adverse drug reactions without a proven benefit. However, all previous studies seemed to ignore the testing of effectiveness of hydrocortisone therapy during its pharmacological effects, which come hours later. On this principle, we aimed to test the effectiveness of intravenous hydrocortisone given 2 h or more prior to the commencement of antivenom therapy to reduce adverse drug reactions to antivenom. In an open-labelled randomized controlled trial, patients with a history of snakebite were randomly assigned to receive either 500 mg intravenous hydrocortisone bolus given 2 h or more prior to antivenom therapy (Group A) or at the time of antivenom therapy (Group B). The primary endpoint was the reduction of adverse drug reactions to antivenom of any grade of severity within the first 48 h. This trial has been registered with the "Sri Lanka Clinical Trials Registry", number SLCTR/2010/005. A total of 236 patients were randomized to group A or Group B. In the group A, 38 participants received hydrocortisone 2 h before administration of antivenom whilst 33 received hydrocortisone less than 2 h before administration of antivenom. In the Group B, 84 participants received hydrocortisone at the time of antivenom therapy. In Group A (n, 38), and Group B (n, 84), 15 patients (39%) and 29 patients (35%) developed reactions respectively and the difference is not significant ($p = 0.598$). Moreover, hydrocortisone therapy did not significantly reduce the occurrence of antievnom reactions of any grade of severity. Further, it didn't delay the occurrence of antivenom reactions in patients who received hydrocortisone either more than 2 h or less than 2 h before the antivenom as opposed to the control group (group B). Intravenous hydrocortisone shows no difference in the timing, rate or severity of adverse drug reactions to antivenom when administered simultaneously and up to 4 h prior to antivenom.

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1. Introduction

Snakebite is a significant health issue in the tropics, mostly affecting rural agricultural communities of the developing countries (Warrell, 2010). Antivenom has been in use in the management of snakebite since its development in 1898 by Albert Calmette in Vietnam (Warrell, 2010). Snake antivenoms are purified immunoglobulins or immunoglobulin fragments of immunized animals with snake venoms. Antivenom first binds to the venom toxins in the circulation and blocks the actions of toxins (Gutierrez et al., 2013). However, apart from the desired therapeutic effects, antivenoms are known to cause adverse drug reactions (ADR)

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including life threatening anaphylaxis at times (Nuchprayoon and Garner, 2009). Various constituents in the antivenom, namely contaminants like endotoxins and viruses, impurities such as proteins other than immunoglobulins of the immunized animal, immunochemical properties of the antivenom were postulated as causes of antivenom reactions (León et al., 2013). Although ADR are not uncommon even with antivenoms of well repute (Isbister et al., 2008), overall incidence of reactions could be minimized by adhering to better manufacturing procedures (Gutiérrez et al., 2011).

Despite questionable accuracy of statistics, over 38,000 hospital admissions due to snakebites are officially recorded in Sri Lanka (Ministry of Health, 2008). Hump-nosed pit vipers (*Hypnale* sp.), Russell's viper (*Daboia russelii*), common krait (*Bungarus caeruleus*), cobra (*Naja naja*), saw-scaled vipers (*Echis carinatus*) and several mildly venomous and non-venomous snake species are responsible for snakebites in Sri Lanka. Of these, Russell's vipers, common krait, cobra, saw-scaled vipers and the *Hypnale* species lead to medically important snakebites (Kularatne, 2013). Over the decades, Sri Lanka has been dependent on imported Indian Polyvalent Antivenom, which is raised against the venoms of Russell's viper, saw-scaled viper, cobra and the common krait inhabit in India. Apart from its low effectiveness (Phillips et al., 1988; Kularatne et al., 2009), the high adverse drug reaction rates associated with Indian Polyvalent Antivenom have been a major challenge in treating snakebite patients in Sri Lanka (De Silva et al., 2002). Reported acute ADR rates due to Indian Polyvalent Antivenom therapy in Sri Lanka ranged from 30 to 81% (De Silva et al., 2011; Gawarammana et al., 2004; Premawardhena et al., 1999; Ariaratnam et al., 2001; Theakston et al., 1990). Of these, life threatening ADR ranged from 8 to 43% (De Silva et al., 2011; Gawarammana et al., 2004; Premawardhena et al., 1999; Isbister et al., 2012). In a randomized controlled trial that involved 1007 snakebite patients from Sri Lanka, 75% had ADR to antivenom serum (AVS), of which 48% were moderate and 43% were severe (De Silva et al., 2011).

Premedications such as adrenaline, hydrocortisone (HCT) and chlorpheniramine are often used in preventing acute ADR due to antivenom therapy (Nuchprayoon and Garner, 2009; León et al., 2013). Benefit of adrenaline in preventing acute ADR due to AVS therapy has been proven in several studies despite concerns about its safety in cardiac co-morbidities (De Silva et al., 2011; Premawardhena et al., 1999). A randomized controlled trial done in Sri Lanka has shown the effectiveness of intravenous HCT infusion (1 g in 300 ml normal saline) given simultaneously with the AVS infusion together with intravenous chlorpheniramine 10 mg bolus, in preventing acute ADR (Gawarammana et al., 2004). On the contrary, in another clinical trial, intravenous HCT bolus of 200 mg given at the starting point of the antivenom infusion, alone or in various combinations with subcutaneous 0.25 mg adrenaline and 25 mg intravenous chlorpheniramine, did not significantly reduce the acute ADR as opposed to the placebo (De Silva et al., 2011). Further, administering HCT said to have negated the benefits of adrenaline in the above study.

In all these trials, the efficacy of HCT in preventing ADR has been evaluated when administrated simultaneously with the AVS (Gawarammana et al., 2004) or as a bolus with the commencement (De Silva et al., 2011) or 30 min before the commencement of AVS therapy (Caron et al., 2009). However, efficacy of HCT in preventing ADR during its therapeutic actions has not been tested so far. It is well known that HCT delivers its pharmacological effects 2–8 h after the intravenous administration and also has a plasma half-life of 90 min (Rang, Dale, Ritter, Moore). Hence, it could be assumed that to get the potential beneficial effects of HCT, it needs to be administered at least 2 h before AVS therapy. In other words, there should be a reasonable time interval created between HCT and AVS doses. The time interval of 2 h may be insufficient to assess the benefit of HCT as the benefit of reduction of ADR might come after 4 h or even after 8 h. But delaying administration of AVS after HCT bolus is not possible as unopposed envenoming for hours could be more harmful to the patient. Therefore, testing of this hypothesis needed meticulous planning adhering to ethical and methodological issues. In this backdrop, the primary aim of this study was to determine whether administering intravenous HCT 500 mg 2 h before the commencement of AVS therapy would reduce the occurrence of ADR as opposed to HCT given simultaneously with AVS.

2. Methods

2.1. Study design and patients

In this open labelled randomized controlled trial, we enrolled patients with snakebite presented to the Teaching Hospital, Anuradhapura (THA), Sri Lanka, a tertiary care centre, during 12th May 2010 to 22nd May 2011. The patients above 12 years of age were eligible after admission to the Emergency Treatment Unit (ETU) of the THA with a history of a proven snakebite. The key exclusion criteria included presence of well-established envenoming signs on admission to THA, treatment with AVS, HCT, adrenaline or antihistamines before admission to THA and history of eczema, urticaria, drug or food allergies. The well-established envenoming included presence of incoagulable blood, neuromuscular paralysis, significant local envenoming, cardiac, renal or myotoxicity either in isolation or in combination (Kularatne, 2013) and were excluded as they needed immediate administration of antivenom.

The standard sample size calculation formula for experimental studies (Pocock, 1983) was used for sample size calculation.

Following criteria were considered in the calculation;

Prevalence of adverse drug reactions due to antivenom is 60% (Kularatne, 2000). Expected reduction of ADR following the intervention (HCT 2 h before AVS) was 30%. Function of α & β was considered as 7.9 (α at 0.05 level and β at 0.2 level). The power considered here was at 80% level.

$$n = \frac{P_1(100 - P_1) + P_2(100 - P_2)}{(P_1 - P_2)^2} * \int (\alpha, \beta)$$

Therefore, the sample size for the study is $= [(60 \times 40) + (30 \times 70)/900] \times 7.9 = 40$ subjects in each arm of the study.

This trial was approved by the Ethical Review Committee, Faculty of Medicine, University of Peradeniya, Sri Lanka and was registered with the Sri Lanka Clinical Trials Registry, number SLCTR/2010/005. The informed consent was obtained from all participants of this study prior to randomisation.

2.2. Randomisation

Eligible patients were randomized to receive a bolus of 500 mg intravenous hydrocortisone at least 2 h prior to the AVS infusion (Group A) or to receive the same dose at the time of AVS administration (Group B). To randomly allocate the patients to two groups, sequentially numbered sealed envelopes containing the information A or B was used in the numbered order. Computer generated randomisation was done in blocks of 20 to assign the

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