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Effect of Pre-Medication on Early Adverse Reactions Following Antivenom Use in Snakebite

A Systematic Review and Meta-Analysis

Abdulrazaq G. Habib

Infectious and Tropical Diseases Unit, Department of Medicine, Bayero University Kano, Aminu Kano Teaching Hospital, Kano, Nigeria

Abstract

Background: Pre-medication has been used to protect against early adverse reactions (EAR) following antivenom administration after snakebite. Studies have evaluated its efficacy with variable results.

Objective: The aim of the study was to conduct a systematic review and meta-analysis of published data to assess the effect of pre-medication on the risk of EAR.

Methods: We conducted a search of MEDLINE, the Cochrane Database and various search engines/websites, searched handbooks, book chapters and peer-reviewed articles relating to clinical snakebite, and consulted experts in this field. The search was on published literature up to September 2010. A meta-analysis was conducted of all randomized and non-randomized studies of EAR following antivenom in snakebite that utilized either adrenaline (epinephrine)-containing or non-adrenaline (antihistamines, corticosteroids)-containing pre-medications compared with control groups. We performed either random- or fixed-effects analysis based on the presence of heterogeneity as assessed with two tests, including the I^2 statistic, and performed restricted analyses on data derived from randomized or non-randomized studies. Sensitivity analysis investigating the influence of single studies on overall estimates was conducted and we determined publication bias where detected in both of the two tests used for its assessment.

Results: Three randomized and four non-randomized studies were selected for inclusion in this study. When all ten comparisons from the seven selected studies were combined (with a total of 434 subjects in the pre-medication groups and 399 subjects in the control groups), the overall summary risk ratio (RR) for EAR was 0.70 (95% CI 0.50, 0.99; $p = 0.041$; $I^2 = 66.5\%$). When analysis was restricted to only studies employing adrenaline-containing pre-medication, the combined summary RR was 0.32 (95% CI 0.18, 0.58; $p < 0.0001$; $I^2 = 9.5\%$). Results were not statistically significant when analyses were

restricted to studies employing non-adrenaline-containing pre-medications, or cohort or randomized controlled designs. Analysis was limited by heterogeneity, paucity and quality of data.

Conclusions: Findings are consistent with a substantial beneficial effect of adrenaline pre-medication, but a marginal benefit with the combination of pre-medications used against EAR could not be excluded. Future studies are recommended and they should explore possible synergism of broader combinations of drugs and effects of mode of antivenom administration in large randomized controlled trials. Meanwhile, highly purified antivenoms with less risk of EAR should be made available in the rural tropics.

Background

Envenoming resulting from snakebites is an important public health problem in many tropical and subtropical agricultural communities, and effective antivenom remains the only specific treatment for snakebite envenoming. Early adverse reactions (EAR) after antivenoms are common, and range from 52% to 81% in incidence in certain parts of the tropics.[1] EAR may be life threatening, potentially leading to anaphylaxis and cardiorespiratory emergency that may necessitate advanced life support. Unfortunately, sensitivity tests are unreliable and have no predictive value for the occurrence of early reactions or even severe systemic anaphylaxis.[2] In areas where snakebites are common, qualified staff and equipment are often lacking in health facilities. With such limited resources, taking steps to safely reduce the risk of adverse antivenom reactions through prophylaxis is desirable. Consequently, a safe, efficacious pre-medication regimen for the prevention of potentially life-threatening anaphylactic reactions would be particularly relevant and important in the management of snakebite in those regions. Traditionally, parenteral adrenaline (epinephrine), hydrocortisone and antihistamines, either chlorpheniramine or promethazine, have been used for pre-medication to prevent EAR following antivenom use with variable results. In 2000, a Cochrane Database systematic review concluded that prophylactic adrenaline might be sensible and antihistamines appeared to have no obvious benefit based on two trials.[3-5] Both trials were criticized for early stoppage before sufficient evidence was accrued.[6] In light of these developments and subsequent published reports,[1,7] a meta-analytical review addressing the question of whether pre-medication prevents against EAR after antivenom use was undertaken and is presented in this study.

Methods

Search Strategy

To build up this meta-analysis, we searched for relevant English-language papers in MEDLINE, the Cochrane Database, other search engines, e.g. 'Google', and several websites. 'Adrenaline', 'anaphylaxis', 'antivenin', 'antivenom', 'chlorpheniramine', 'clinical trial', 'diphenhydramine', 'early adverse reactions (EAR)', 'envenoming', 'envenomation', 'hydrocortisone', 'hypersensitivity', 'immediate reactions', 'pre-medications', 'prevention', 'promethazine', 'prophylaxis', 'reactions', 'snakebite' and 'studies' were used in various combinations as primary search keywords with no period or regional restriction. The search was on published literature up to September 2010. We also used our own knowledge, experience, discussions with colleagues and recognized experts, as well previous publications on the subject. When required, we contacted authors and also manually searched the reference lists of all identified publications and recent systematic reviews. Books, chapters and review articles on clinical snakebite were consulted.

Selection Criteria

We reviewed the full text of all accessible English-language studies evaluating or reporting

on the prevention of early EAR following antivenom use after snakebite, applying the following inclusion criteria: (i) studies that compared the risk of EAR in snakebite victims who received antivenoms and pre-medication versus control groups, defined as placebo or no pre-medication; (ii) studies that were randomized controlled trial (RCT) or cohort study designs; and (iii) when pre-medication drugs were named. Studies that did not fulfil inclusion criteria, had insufficient and/or lacked desired information were excluded. Data ascertained and extracted included study details, i.e. study participants, size, site, date, snake responsible for bite, design, antivenom administered, pre-medication intervention drug regimen, definition/monitoring of EAR, other outcomes recorded, and quality measures (e.g. study conduct, blinding, duration, validation of antivenom and EAR). For the RCTs, Jadad scores were further calculated to estimate their quality and validity.[8]

Statistical Analysis

We determined the risk of EAR as the number of patients who developed EAR divided by the total number of snakebite patients administered antivenom separately for the pre-medication group and control group for each study. Risk ratio (RR) and respective 95% CIs for EAR in the pre-medication group compared with the control group were calculated for each study. The log RR and the standard error of log RR were computed for each trial. Individual studies with data that could be categorized into adrenaline-containing, adrenaline-excluding or other mutually exclusive pre-medication groups were analysed as separate substudies or comparisons as pre-specified.

We evaluated for statistical heterogeneity by conducting tests of between-study heterogeneity and by using the I^2 statistic; $I^2 > 50\%$ denotes substantial heterogeneity.[9] Meta-analyses were carried out to derive summary RRs by using either a random-effects model (REM) or fixed-effects model (FEM). When evidence of heterogeneity was found, indicative of large between-study variance, the former was presented, with corresponding p-values derived from tests for heterogeneity denoted as P_{het}.[10,11] In the meta-analysis, all studies were first considered as a single group. Subsequently, four separate meta-analyses were carried out with studies restricted to only RCTs, non-randomized cohort or comparative studies, and studies containing or excluding adrenaline pre-medications.

Sensitivity analyses primarily consisted of investigating the influence of a single study on the overall meta-analysis, with resulting estimates computed, omitting one study in each turn and evaluating estimates of the remaining studies numerically and graphically as described elsewhere.[12] Publication bias was investigated using funnel plots derived from Begg and Mazumdar[13] adjusted rank correlation tests based on Kendall's tau (with continuity correction) [referred to as Begg's test] and the regression asymmetry test of Egger et al.[14] Given the limitations of funnel plot,[15] publication bias is only confirmed when detected in both the two tests used for its assessment. All analyses were carried out using Stata version 11.0 (Stata Corp., College Station, TX, USA). The MOOSE (Meta-analysis Of Observational Studies in Epidemiology) and QUORUM (QUality Of Reports of Meta-analyses) statements guided our reporting and discussion of the results.[16,17]

Results

Overview of Included Studies

Of the 154 abstracts and articles, we identified 17 articles that dealt with pre-medication, snakebite and antivenom EAR. Many were not directly relevant to the review question and were excluded. Of the 17 selected, 7 were deemed to be non-comparative case reports or case series possessing insufficient information for determining relevant groups, or not directly responding to the review objective.[18-24] A further three articles were excluded as they were commentaries or letters.[6,25,26] The remaining seven studies were selected and appraised individually, and published data from the studies were included in the analysis (figure 1; table I).[1,3,4,7,27-29] Three of these seven studies were RCTs[1,3,4] (mean Jadad score of 4.33 for all three RCTs[8]) and two were the subject of a prior systematic review.[3-5]

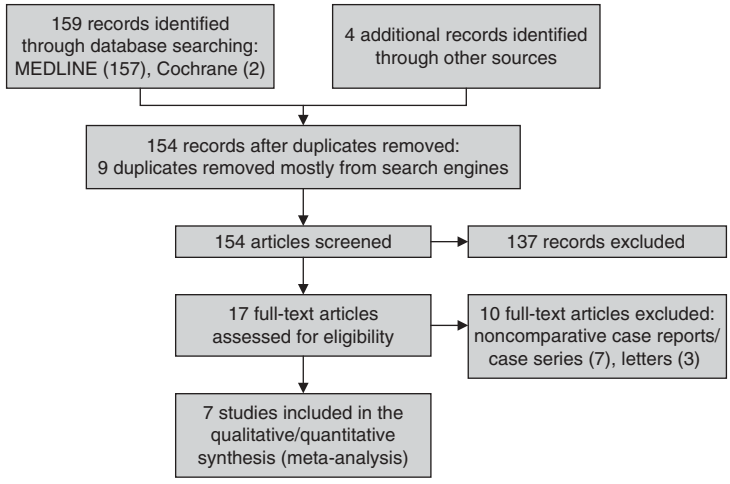

Fig. 1. Flow diagram of the process of article selection for meta-analysis.

Data extracted from patients in three of the seven studies (Gawarammana et al.,[1] Williams et al.[27] and Isbister et al.[28]) [table I] could be categorized into recipients of adrenaline-containing, adrenaline-excluding or other mutually exclusive pre-medication groups, and each was analysed as a separate comparison or substudy identified as (a) and (b) based on their respective interventions. When all seven studies were combined, a total of 434 and 399 subjects were included in the pre-medication and control groups, respectively.

Children younger than 12 years of age were not recruited in two RCTs,[1,4] but three studies[3,27,29] included children in this age group. The age of the youngest participant could not be discerned in the study by Isbister et al.[28] The ages of participants ranged from <1 year to 70 years in the study by Caron et al.[7] Actual ages of participants could not be linked to individual intervention assignments, especially in the cohort studies.

Interventions were administered parenterally; adrenaline was administered subcutaneously (in a few cases intramuscularly), chlorpheniramine was administered intravenously (bolus), diphenhydramine intravenously, hydrocortisone intravenously (bolus and infusion) and promethazine intramuscularly and intravenously. The dose of adrenaline used was 0.25–0.5 mL of a 1 : 1000 solution. In subgroups who received non-adrenaline containing pre-medications, actual numbers of individuals receiving any particular drug were not always decipherable into mutually exclusive categories in the studies from Australia and Papua New Guinea.[27,28] No information on pre-medication was provided in 69 of 195 (35.4%) patients in the study by Isbister et al.[28] These could serve as sources of bias.

Snakebites recorded varied by study location, with *Bothrops* spp. being found mainly in Brazil and Ecuador, and Hump-nosed and Russell's vipers, and Cobra and Krait species predominating in Sri Lanka. Snakebites recorded from the Australian study originated from the Brown, Tiger, Black, Death Adder and Taipan species; the snake species responsible were not mentioned in the study from Papua New Guinea but the antivenoms supplied or used had coverage against Death Adder, Black snake and Taipan envenoming.[27]

The assessment, definition, features and severity grading of envenoming varied across studies; systemic envenoming included coagulopathy, neuromuscular complications, renal impairment and combinations of these features. Antivenoms used in the studies included the better refined Commonwealth Serum Laboratories [CSL] Ltd antivenoms (Australia), Instituto Butantan Fundacao antivenoms (Brazil), Instituto Vital antivenoms (Brazil), lyophilized Haffkine polyspecific

Table I. Summary of studies comparing pre-medication with placebo (PL) or no treatment in preventing immediate reactions following antivenom use in snakebite

Study, y (country, commencement date)	Design	Interventions	No reactions/ total (%) in two comparative arms	RR (95% CI)	Potential risk for bias
Premawardhena et al.,[4] 1999 (Sri Lanka, 1998)	Randomized, double-blind, PL-controlled	Adrenaline (epinephrine) SC vs PL	6/56 (10.7) vs 21/49 (42.9)	0.25 (0.11, 0.57)	Patients at high risk for adrenaline adverse effects were excluded
Fan et al.,[3] 1999 (Brazil, 1994)	Sequential randomized, double-blind, PL-controlled	Promethazine IM vs PL	12/49 (24.5) vs 13/52 (25.0)	0.98 (0.50, 1.94)	Low risk of confounding because of randomized design
Gawarammana et al.,[1] 2004a (Sri Lanka, 2002)	Randomized, double-blind, PL-controlled	Hydrocortisone IV vs PL	12/15 (92.3) vs 13/16 (81.3)	0.98 (0.70, 1.39)	Premature trial stoppage. Low statistical power from small sample size
Gawarammana et al.,[1] 2004b (Sri Lanka, 2002)	Randomized, double-blind, PL-controlled	Hydrocortisone + chlorpheniramine vs PL	11/21 (52.4) vs 13/16 (81.3)	0.64 (0.40, 1.03)	Premature trial stoppage. Low statistical power from small sample size
Williams et al.,[27] 2007a (Papua New Guinea, 1994)	Retrospective cohort	SC adrenaline-containing vs no pre-medication[a]	5/65 (7.7) vs 7/25 (28.0)	0.27 (0.10, 0.79)	Potential confounding – adrenaline group also received other agents. EAR may have been missed as non-urticarial type often unrecognized. Low quality of medical records in rural areas
Williams et al.,[27] 2007b (Papua New Guinea, 1994)	Retrospective cohort	Non-adrenaline-containing pre-medications vs no pre-medication[a]	13/46 (28.3) vs 7/25 (28.0)	1.01 (0.46, 2.20)	EAR may have been missed as non-urticarial type often unrecognized. Low quality of medical records in rural areas
Isbister et al.,[28] 2008a (Australia, 2002)	Nested cohort	SC adrenaline-containing vs no pre-medication[b]	2/11 (18.2) vs 20/86 (23.3)	0.78 (0.21, 2.90)	Potential confounding – adrenaline group also received other agents. No information on pre-medication in one-third of patients
Isbister et al.,[28] 2008b (Australia, 2002)	Nested cohort	Non-adrenaline-containing pre-medications vs no pre-medication[b]	9/29 (31.0) vs 20/86 (23.3)	1.33 (0.69, 2.59)	No information on pre-medication in over one-third of patients
Seneviratne et al.,[29] 2000 (Sri Lanka, 1997)	Prospective cohort	Non-adrenaline-containing pre-medications vs no pre-medication[c]	47/89 (52.8) vs 55/95 (57.9)	0.91 (0.70, 1.18)	ND
Caron et al.,[7] 2009 (Ecuador, 1997)	Historical cohort	Hydrocortisone + diphenhydramine vs no pre-medication	1/53 (1.9) vs 37/76 (48.7)	0.04 (0.01, 0.27)	The two groups not strictly similar. Control group evaluated retrospectively and intervention group prospectively. Different antivenom administration methods

a Non-adrenaline-containing pre-medications included promethazine and hydrocortisone in various combinations, while adrenaline-containing pre-medications included adrenaline alone or with the same drugs in various combinations.

b Non-adrenaline-containing pre-medications included promethazine and hydrocortisone in various combinations, while adrenaline-containing pre-medications included adrenaline alone or with the same drugs in various combinations.

c Non-adrenaline-containing pre-medications included hydrocortisone alone or with either chlorpheniramine or promethazine.

EAR = early adverse reactions; **IM** = intramuscularly; **IV** = intravenously; **ND** = no data; **RR** = risk ratio; **SC** = subcutaneous.

antivenoms (Haffkine, India) and lyophilized polyspecific antivenoms (VinsBioproducts, India). All are Fab2 fragments of equine origin. In some studies, test dose was used prior to antivenom administration.

Similarly, the assessments, features and severity grading used for defining EAR varied between studies. Two studies (Caron et al.[7] and Isbister et al.[28]) used a detailed definition of EAR described elsewhere.[30] However, in general, combinations of pruritis, skin rash with or without pruritis, urticaria, fever, rigors, nausea, vomiting, abdominal pains, angioedema, facial oedema, cough, rhonchi, bronchospasm with or without cyanosis/stridor and changes in blood pressure, electrocardiography, heart rate or respiration were used in defining EAR; in various gradations these were categorized as mild, moderate or severe EAR. Overall, definitions were clearer and more complete in the randomized studies.[1,3,4]

Two studies explored the safety of adrenaline pre-medication; however, none of the patients who received this pre-medication developed a sustained increase in blood pressure or features of intracranial haemorrhage, even though 26/56 (46.4%)[4] and 47/65 (72.3%)[27] had evidence of coagulopathy, respectively. A patient in the latter study developed transient tachycardia.[27]

Risk Ratio of Early Adverse Reactions in the Meta-Analyses

The summary RR for all ten comparisons from the seven studies combined was 0.70 (95% CI 0.50, 0.99; $p = 0.041$; $I^2 = 66.5\%$) in an REM as there was also strong evidence of heterogeneity ($P_{het} = 0.001$) [figure 2], although the FEM estimate clearly achieved statistical significance (0.83 [95% CI 0.70, 0.97; $p = 0.023$]). In eight of the ten comparisons, the point estimate of RR was <1 and this was statistically significant in three of the comparisons, including two that evaluated the effect of adrenaline on EAR. When single studies were excluded in turn, similar overlapping estimates were found (figure 3). The funnel plot (figure 4) suggested little evidence of publication bias ($p = 0.049$ and $p = 0.071$ using Begg's and Egger's tests, respectively).

Restricting analysis to only studies employing adrenaline-containing pre-medication found the summary RR from the three studies combined was 0.32 (95% CI 0.18, 0.58; $p < 0.0001$; $I^2 = 9.5\%$) in an FEM as there was no evidence of heterogeneity ($P_{het} = 0.331$) [figure 5]. Excluding individual studies gave similar FEM estimates. The funnel plot suggested no evidence of publication bias ($p = 0.296$ and $p = 0.295$ using Begg's and Egger's tests, respectively).

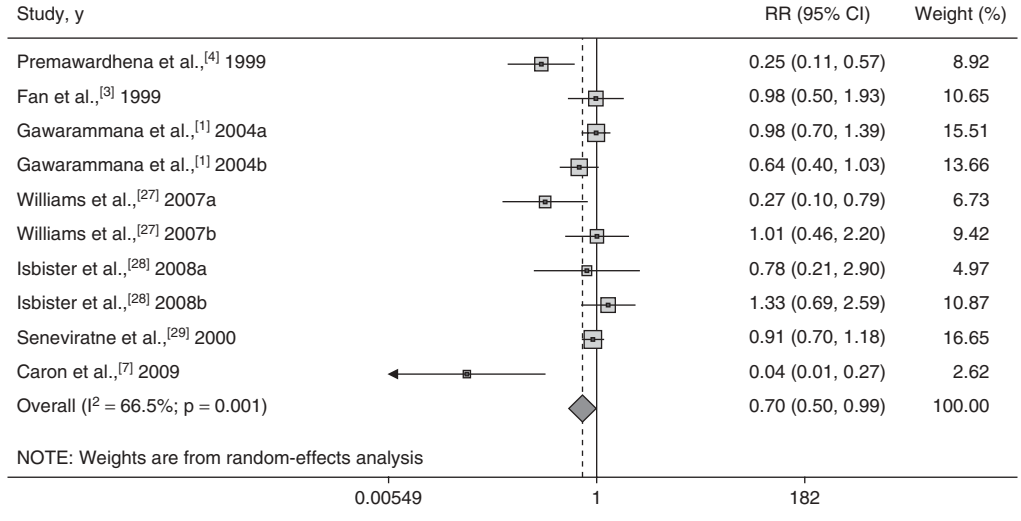

Fig. 2. Relative risk of immediate reactions associated with pre-medication after antivenom use following snakebite in ten comparisons from seven studies. **RR** = risk ratio

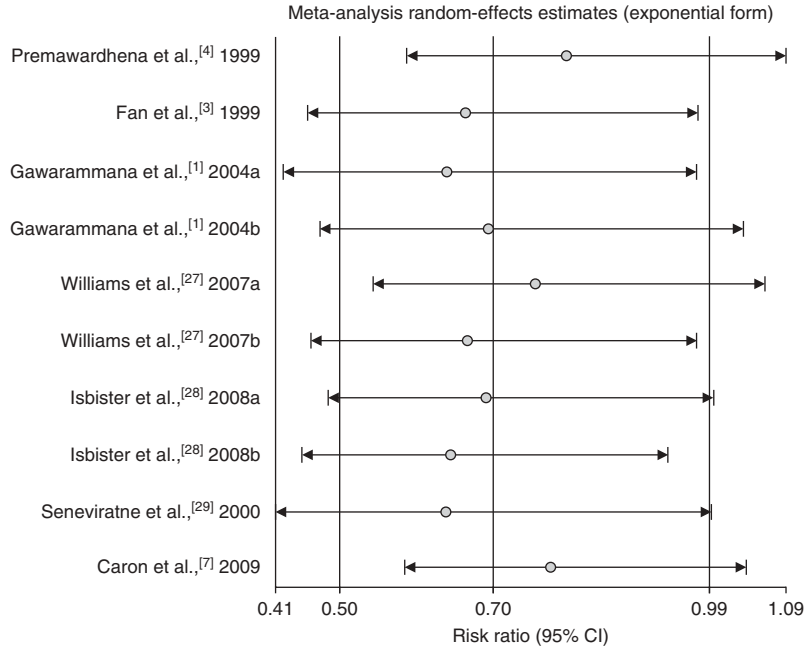

Fig. 3. Sensitivity analyses showing effect of dropping individual studies in turn on pooled (random effects) risk ratio estimates of the remaining nine studies (combined estimates from the ten comparisons are depicted by the three vertical lines).

When the analysis was restricted to studies employing non-adrenaline-containing pre-medications only, the summary RR for seven comparisons from six studies combined was 0.87 (95% CI 0.64, 1.18; $p = 0.364$; $I^2 = 56\%$) in an REM estimate as there was evidence of heterogeneity ($P_{het} = 0.034$) [figure 6]. Excluding individual studies gave similar overlapping estimates. The funnel plot suggested no evidence of publication bias ($p = 0.764$ and $p = 0.287$ using Begg's and Egger's tests, respectively).

When the analysis was restricted to RCTs only, the summary RR for four comparisons from three studies combined was 0.68 (95% CI 0.41, 1.12; $p = 0.127$; $I^2 = 70.5\%$) in an REM as there was strong evidence of heterogeneity ($P_{het} = 0.017$), although an FEM gave a similar estimate (figure 7). Excluding individual studies gave similar estimates. The funnel plot suggested no evidence of publication bias ($p = 0.308$ and $p = 0.295$ using Begg's and Egger's tests, respectively).

When the analysis was restricted to cohort studies only, the summary RR for six comparisons from four studies combined was 0.67 (95% CI 0.37, 1.20; $p = 0.175$; $I^2 = 69.2\%$) in an REM as there was evidence of heterogeneity ($P_{het} = 0.006$), although an FEM gave a similar estimate. Excluding individual studies gave similar estimates.

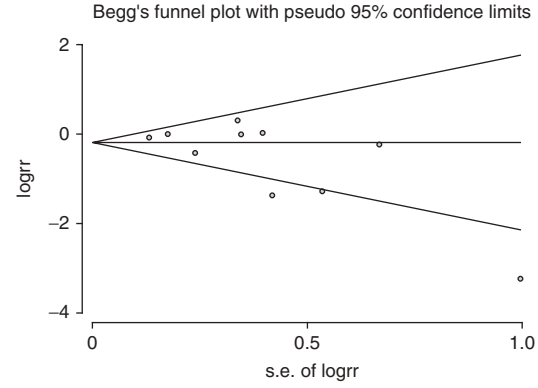

Fig. 4. Funnel plot to detect publication bias for studies reporting the effect of pre-medication on the risk of immediate reaction to antivenoms used following snakebite in ten comparisons from seven studies. **logrr** = log risk ratio; **s.e.** = standard error.

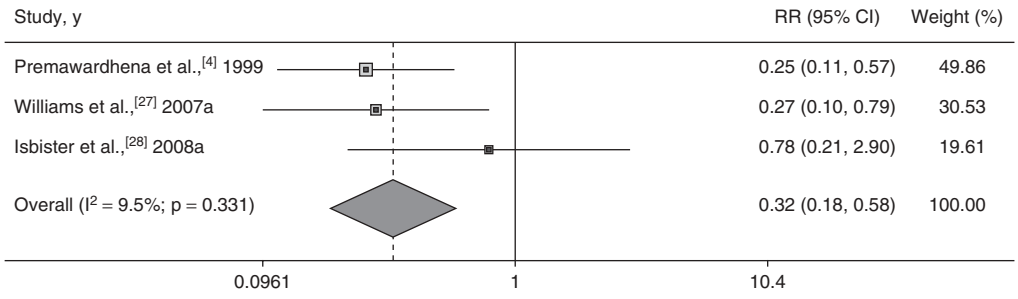

Fig. 5. Relative risk of immediate reactions associated with adrenaline (epinephrine) pre-medication prior to antivenom use following snakebite in three studies. **RR** = risk ratio.

The funnel plot suggested little or no evidence of publication bias ($p = 0.06$ and $p = 0.228$ using Begg's and Egger's tests, respectively).

Discussion

The overall summary RR for EAR after pre-medication combinations is statistically significant, and the point estimate and boundaries of the 95% CI suggest that a slight benefit cannot be excluded; however, this study highlights the limitations and paucity of existing data. Restricting the analysis to studies employing non-adrenaline containing pre-medications or to cohort or RCTs shows a lack of beneficial effect using appropriate statistical methods.

Studies using either antihistamine or corticosteroid pre-medications alone failed to show any beneficial effects.[1,3] Fan et al.[3] found no protection against EAR conferred by intramuscular promethazine administered 15–20 minutes prior to antivenom, and suggested that promethazine does not block histamine H_2 receptors, which may play an important role in anaphylaxis. Indeed, a human study has compared H_1 plus H_2 blockade with only H_1 blockade for the management of mild allergic reactions, and found a small benefit with the combined antihistamine approach.[31]

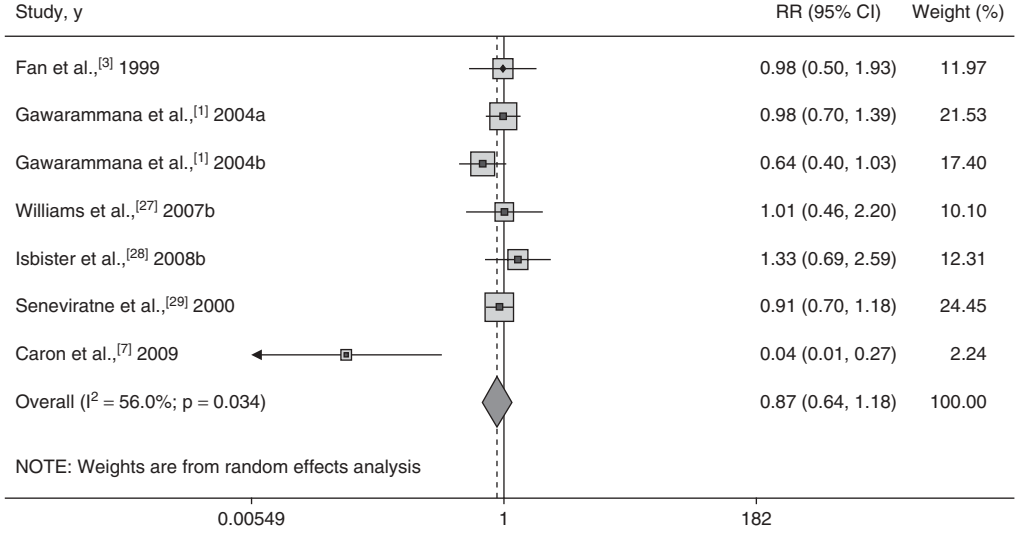

Fig. 6. Random effects risk ratio of immediate reactions associated with non-adrenaline (epinephrine) pre-medication prior to antivenom use following snakebite in seven comparisons from six studies. **RR** = risk ratio.

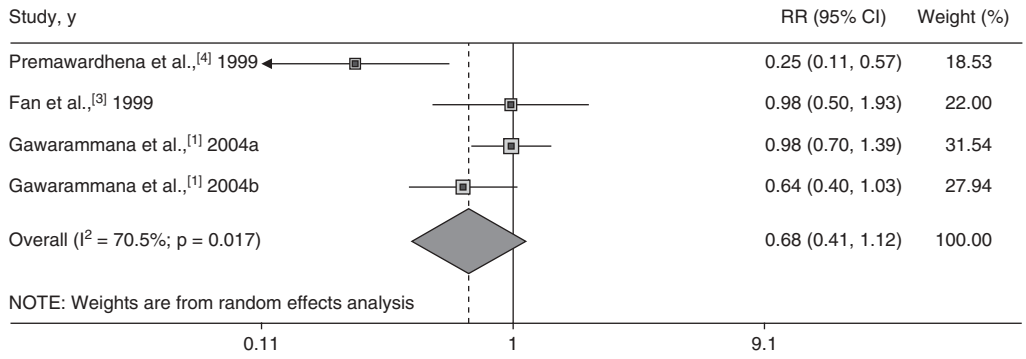

Fig. 7. Effect of pre-medication on risk ratio (RR) [random effects] of immediate reaction to antivenoms used following snakebite in four comparisons from three randomized controlled trials employing adrenaline (epinephrine) [one] and non-adrenaline (three) pre-medications. **RR** = risk ratio.

None of the studies with non-adrenaline-containing pre-medications utilized H_2 blockade, and collectively these studies failed to report measurable protective effect against EAR. Although hydrocortisone together with diphenhydramine, an H_1 receptor antagonist, was 96% protective against EAR when compared with historical controls,[7] it was not protective when combined with chlorpheniramine, also an H_1 antagonist.[1] This suggests future studies should employ corticosteroids combined with both H_1 and H_2 blockade. As corticosteroids take longer to act, their potential impact on late serum reactions should also be investigated in such studies.

The combined summary RR for adrenaline pre-medication was significant; it conferred approximately 68% protection against EAR and the benefit was reported in two of the three comparisons that used CSL and Haffkine antivenoms for management.[4,27] The beneficial effect we have reported is greater and more robust compared with the earlier Cochrane Database systematic review, which was based on fewer studies.[5]

Concerns have been raised that adrenaline-induced hypertension might precipitate intracranial haemorrhage in envenomed patients with coagulopathy, but no such events were observed in this study. In a previous report, low-dose subcutaneous adrenaline only caused a few cases of local haematoma and did not cause significant changes in heart rate or blood pressure.[24] However, three possibly unrelated incidental cases of intracranial haemorrhage have been reported following use of subcutaneous adrenaline pre-medication[24,27] and caution should be exercised before its administration, and appropriate monitoring put in place thereafter.

Adrenaline pre-medication should be avoided in very young children, pregnant women and patients with venom-induced coagulopathy who have altered consciousness, meningeal irritation or focal deficit. It can potentially protect against life-threatening anaphylaxis in resource-constrained tropical settings where antivenom EARs are high and facilities for mechanical ventilation are lacking. In rural African Savannah and South America where *Echis* and *Bothrops* species are important causes of coagulopathy and the incidence of EAR reach over 6–25%,[3,32,33] adrenaline pre-medication would probably be beneficial but should be used cautiously. Large randomized, placebo-controlled, multicentre trials in envenomed patients with coagulopathy are required to establish its efficacy, safety and potential synergy with other interventions in such settings.

Some of the reviewed studies were observational and EAR might be lower than actual because of underreporting. For instance, lack of information on pre-medication in over one-third of patients in the study reported by Isbister et al.[28] could have led to residual bias. Second, it is also important to recognize that studies from Australia and Papua New Guinea involved a high-quality antivenom[27,28] and, except in a few cases, the majority of adverse events were either cutaneous or pyrogenic, indicating that they were

less severe than reactions seen in other settings, where relatively low-quality antivenoms that cause a high proportion of more severe adverse events (including anaphylaxis) are used. Therefore, the effect of pre-medication in reducing EAR becomes subtle and probably much less dramatic in settings using refined antivenoms. In Ecuador, slow infusion of antivenom and pre-medication over 1 hour compared with intravenous push injection reduced both the frequency as well as severity of EAR, although the 'historical' control group may not be strictly comparable to the intervention group.[7]

Publication bias is unlikely to have affected the results of our analysis as most of the studies reviewed did not report positive results, which, compared with negative studies, are more likely to be published. Furthermore, using multiple approaches our analyses suggested that publication bias did not affect the summary estimates; however, publication bias from non-inclusion of literature in other languages is unclear, although is likely to be minimal.

There are several sources of heterogeneity in the reviewed studies, including differing definitions and severity of reactions, manifestations of envenoming among patients, pre-medications, study designs, and antivenom quality and type. This heterogeneity provides some advantages from the point of view of generalizability of findings to diverse patient populations.[10,11] Traditionally, a meta-analysis is conducted on data obtained from RCTs, but can also be conducted on data obtained entirely from non-interventional studies[10,11,17,34] and occasionally even on data obtained from both non-randomized and randomized studies combined, especially when data are sparse,[35-37] as in this case. In such instances, the combinability of studies poses special challenges, but given the marginal beneficial effects reported after combining the studies, the approach has the added advantage of generating hypotheses for testing in the future, e.g. testing combinations of pre-medications. Furthermore, we conducted restricted sub-analyses on data obtained from non-randomized and randomized studies using different pre-medications separately to address these challenges. Other limitations include poor reporting of EAR, the small sample size of most studies and the diverse methodological quality of studies. A detailed account of such diverse methodological and reporting discrepancies in clinical studies on snakebite was recently published.[38]

However, these limitations do not diminish the public health significance of the findings of this study, the importance of which rests on the challenges of clinical management of snakebite, in particular the ensuing EAR following administration of antivenoms in the rural tropics. These reactions can lead to anaphylaxis, respiratory failure and shock, all potentially fatal conditions. In developed countries where facilities for intensive care, mechanical ventilation and advanced life support are available, immediate reactions, when promptly recognized, can be managed appropriately and successfully. Snakebite, however, is a neglected problem prevalent in the resource-limited agricultural communities where such facilities are generally lacking; the findings of this study should be viewed in this context. Thus, it is recommended that, when judged safe, adrenaline pre-medication should be considered, especially in settings where highly purified (minimally reactogenic) antivenoms are lacking. Finally, use of pre-medications adds complexity, cost and further safety concerns, and it would be advantageous to continue to promote highly purified antivenoms with less risk of EAR in resource-constrained settings.

Conclusions

This study is limited by heterogeneity and paucity of data but findings are consistent with substantial beneficial effect of adrenaline pre-medication, and slight and marginal benefit with other combinations of pre-medications (injectable antihistamines and corticosteroids) used against EAR could not be excluded. However, diverse methodological and reporting discrepancies are apparent in the published studies on which these conclusions are based. Future studies are recommended that should explore the possible synergism of broader combinations of drugs and effects of mode of antivenom administration in large RCTs among defined populations. Meanwhile,

highly purified antivenoms with less risk of EAR should be made available in the rural tropics.

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Correspondence: Professor *Abdulrazaq G. Habib*, Infectious and Tropical Diseases Unit, Department of Medicine, Bayero University Kano, Aminu Kano Teaching Hospital, PMB 3452, Kano, Nigeria.
E-mail: abdulrazaq_habib@yahoo.co.uk