Medically Significant Late Bleeding After Treated Crotaline Envenomation: A Systematic Review

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Study objective: We estimate the proportion of patients with crotaline snake envenomation who are treated with Crotalidae polyvalent immune Fab (ovine) antivenom and who develop medically significant late bleeding.

Methods: We performed a systematic review of all published cohort studies of North American crotaline snake envenomation patients treated with Fab antivenom. We searched PubMed, Ovid MEDLINE, and EMBASE from January 1, 1997, to April 30, 2012. Data were extracted by 2 trained researchers. Late bleeding was defined as bleeding that began or recurred after initial control of the envenomation syndrome. Medically significant late bleeding was defined a priori as late bleeding treated with RBC transfusion, vasoactive drug infusion, surgery, or rehospitalization or associated with a hemoglobin decrease of greater than or equal to 3 g/dL, hematocrit decrease of greater than or equal to 8%, disability, or death. Summary incidence and 95% confidence intervals (CIs) were calculated with a random-effects Poisson regression model.

Results: Nineteen unique cohort studies were identified. Four studies collected data prospectively, and in 9 studies, patients were followed actively after hospital discharge. A total of 1,017 subjects were enrolled in these cohort studies. Late bleeding was reported in 9 subjects (0.9%; 95% CI 0.4% to 2.2%), of whom 5 subjects (0.5%; 95% CI 0.1% to 1.7%) had medically significant late bleeding. Three patients received RBC transfusion; no deaths or permanent sequelae were reported. Estimates of risk may be affected by underreporting.

Conclusion: Medically significant late bleeding appears to be uncommon in snakebite victims treated with Fab antivenom. [Ann Emerg Med. 2014;63:71–78.]

Please see page 72 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Approximately 9,000 patients are treated in US emergency departments (EDs) for snake envenomation each year.[1] More than 95% of these envenomations involve pit viper snakes (family Viperidae, subfamily Crotalinae, genera *Crotalus* [rattlesnakes], *Sistrurus* [pygmy rattlesnakes], and *Agkistrodon* [copperhead and moccasin snakes]). Crotaline snake envenomation can cause local tissue injury, systemic venom effects, and hematologic venom effects, which consist primarily of fibrinogen degradation and platelet destruction.[2] Although these hematologic venom effects can cause bleeding, the proportion of patients who experience medically significant bleeding is not known.

The only currently Food and Drug Administration–approved antivenom available for the treatment of crotaline snakebite in the United States is Crotalidae polyvalent immune Fab (ovine) (CroFab; BTG International, West Conshohocken, PA; hereafter, FabAV). The proportion of snakebite patients treated with antivenom has increased steadily since the introduction of FabAV in October 2000. In 2010, approximately 70% of crotaline snake envenomation cases reported to US poison centers were treated with FabAV.[3]

In most cases, treatment with FabAV is followed by rapid improvements in venom-induced alterations in fibrinogen levels, prothrombin time, and platelet counts.[4-6] However, recurrence or delayed onset of hematologic venom effects is common. In 3 prospective studies of this phenomenon involving primarily rattlesnake victims, recurrent or delayed-onset hematologic venom effects were observed in 21% to 61% of patients followed.[7-9] Although most cases involve modest decreases in circulating fibrinogen levels or platelet counts, profound coagulopathy and thrombocytopenia have been described. Fatal hemorrhage from recurrent defibrinogenation has been described.[10]

Importance

Late bleeding events are a feared but rare outcome after FabAV treatment of crotaline snake envenomation. Understanding the risk of medically significant late bleeding

Editor's Capsule Summary

What is already known on this topic

Despite nearly 9,000 snake bites treated in US emergency departments each year, late bleeding events are poorly described.

What question this study addressed

This systematic review of 19 cohort studies examined the incidence of medically significant late bleeding in patients treated with Fab antivenin.

What this study adds to our knowledge

Only 5 of 1,017 patients met a priori–defined inclusion criteria for serious late bleeding events. Although no deaths occurred in the cohort studies, they have rarely been reported.

How this is relevant to clinical practice

The incidence of serious late bleeding appears low. Limitations in study data do not permit identification of risk factors or modifications to current antivenin dosing recommendations.

may be important in determining FabAV dosing, laboratory monitoring, hospital discharge criteria, and patient counseling.

Goals of This Investigation

In this systematic review, we synthesize data from published cohort studies to estimate the risk of medically significant late bleeding in patients treated with FabAV.

MATERIALS AND METHODS

Study Design and Setting

This is a systematic review of previously published cohort studies. Retrospective observational studies, prospective observational studies, and clinical trials were eligible for inclusion. Because of the natural range of snake species among patients treated with FabAV, only studies that occurred in the US were included. No restriction was placed on study setting; therefore, studies based in EDs, hospital inpatient units, outpatient centers, poison centers, and combinations thereof were all considered.

Selection of Participants

We searched PubMed, Ovid MEDLINE, and EMBASE to identify all published cohort studies containing primary data about North American human crotaline snake envenomation treated with FabAV. All searches were performed on May 2, 2012, included references dated January 1, 1997, through April 30, 2012, and used search terms that are presented in Appendix E1, Table A1 (available online at http://www.annemergmed.com). This date range was chosen to include the FabAV phase 2 clinical trial, which is the first known publication describing human use of FabAV.[5] In addition, we searched conference proceedings from 2 major toxicology conferences (the North American Congress of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists), the Cochrane CENTRAL registry of clinical trials, www.clinicaltrials.gov, the institutional article files of the Rocky Mountain Poison and Drug Center, and the bibliographies of included studies. The results of the search were not restricted to article type. All searches were performed by a trained researcher (V.K.).

All citations identified from the search strategy were imported into an EndNote database (version X4, Thompson Reuters, Philadelphia, PA). Duplicates were removed, and an electronic filter was used to remove references containing the key words "mouse," "rat," "cellular," "in vivo," or "in vitro."

Two researchers with experience in snakebite literature evaluation (E.J.L., V.K.) reviewed the titles and abstracts of all references to identify any article that might be a cohort study including more than 1 crotaline snake envenomation patient treated with FabAV. Full-text copies of all articles identified by either reviewer were obtained, and data about the design, population, and results of each study were abstracted to a standardized data collection form. Practice abstraction of test articles was used to improve form and abstractor performance before full data abstraction. Discrepancies between the abstractors were identified and resolved by discussion. Verified data were entered into a REDCap database (version 4.8.2, Research Electronic Data Capture, Vanderbilt University, Nashville, TN) and exported to SAS version 9.2 (SAS Institute, Inc., Cary, NC) for analysis.

Outcome Measures

All late bleeding events reported in any study were abstracted and are further described here. A late bleeding event was defined as blood loss that was first noted after initial control of the envenomation syndrome, as defined by the study author or using standard criteria, was achieved.[6,11-13] If initial control of the envenomation syndrome was not achieved or not clearly documented, any bleeding event that was first noted after the first dose of FabAV was administered was considered to be a late bleeding event. A decrease in hemoglobin or hematocrit levels was considered to be a late bleeding event if presented as such by the original study author. All late bleeding events were reported, regardless of the severity of any associated coagulopathy or thrombocytopenia or the interval between initial control and the onset of bleeding. No attempt was made to formally evaluate late coagulopathy or thrombocytopenia in the absence of late bleeding.

Medically significant late bleeding was defined a priori as any bleeding event associated with hypotension (systolic blood pressure $<$90 mm Hg, or appropriate pediatric norms[14]), significant tachycardia (pulse rate $>$140 beats/min or appropriate pediatric norms), a decrease in hemoglobin level greater than or equal to 3 g/dL or a decrease in hematocrit level greater than or equal to 8 g/dL from previously measured levels,

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