Pressure-Immobilization Bandages Delay Toxicity in a Porcine Model of Eastern Coral Snake (Micrurus fulvius fulvius) Envenomation

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Study objectives: Pressure-immobilization bandages are used in countries where neurotoxic snake envenomations are common. They impede lymphatic egress from the bite site and delay systemic venom toxicity. The effectiveness of these devices has not been evaluated in coral snake envenomations. We investigated the efficacy of pressure-immobilization bandages in delaying the onset of systemic toxicity in a porcine model of coral snake envenomation.

Methods: A randomized controlled trial of pressure-immobilization bandages was conducted in a university animal care center. Subjects were 12 anesthetized, spontaneously breathing pigs, ranging from 9.1 to 11.4 kg. After injection with 10 mg of Micrurus fulvius fulvius venom in the subcutaneous tissue of the distal foreleg, subjects were randomized to receive no treatment or application of a pressure-immobilization bandage at 1 minute after injection. Treated animals had elastic bandages applied to the extremity and splinting for immobilization. Vital signs and quality of respirations were recorded. Outcome was the onset of respiratory failure or survival to 8 hours. Necropsies and histologic analysis of the envenomation site was performed.

Results: One animal from each group was removed because of the discovery of pre-existing respiratory pathology. Four of 5 pigs in the treatment group survived to 8 hours, but none in the control group survived. Mean time to onset of respiratory compromise was 170.4 ± 33.3 minutes in the control group. None of the pigs had histologic changes at the envenomation site consistent with ischemia or pressure-related injury.


INTRODUCTION

The North American coral snakes (Micrurus fulvius ssp.) are elapid snakes endemic to the United States that cause fatal human envenomations. These snakes are found from Texas to North Carolina and as far north as Arkansas. An average of 70 reports involving coral snake bites were received by United States poison control centers annually in the past 5 years.1-5 The incidence of reported bites has been increasing, and in 2002 there were 97, the most ever recorded.1-20 The mortality rate of untreated envenomations is reported to be near 10%, although no deaths have occurred in the United States since antivenom was introduced in 1967.21,22

The venom of M. fulvius contains low-molecular-weight peptides that block postsynaptic acetylcholine receptors.23 The venom lacks significant proteolytic activity, and local effects are minimal to none. In severe, untreated envenomations, an asymptomatic period is followed by neuromuscular blockade and fatal respiratory muscle paralysis. Wyeth North American coral snake antivenom has remained the definitive treatment for Micrurus envenomations but is less effective if administered after the onset of paralysis. Production ceased in 2001, and there is no alternative product licensed for use in the United States.24 The company does retain limited emergency stocks of the product.24

Pressure-immobilization techniques, recommended for elapid bites in Australia, impede lymphatic return to the central circulation, thereby sequestering the venom near the bite site and delaying systemic toxicity,25-27 which allows more time to access definitive care in the form of antivenom and advanced airway management. These devices are not tourniquets and are designed to preserve arterial and deep venous flow.
Editor’s Capsule Summary

What is already known on this topic
Pressure-immobilization bandages are effective in the treatment of snake bites found outside the United States.

What question this study addressed
Whether pressure-immobilization bandages would work with envenomations from the Eastern coral snake (Micruroides fulvius fulvius) indigenous to the United States.

What this study adds to our knowledge
Assuming that the porcine model is appropriate, this study provides compelling evidence that the pressure-immobilization bandages are effective.

How this might change clinical practice
Pressure-immobilization technique is a reasonable intervention for coral snake bites in the United States.

Three variations of this concept have been studied. The “Commonwealth Serum Laboratories method” (Commonwealth Serum Laboratories, Parkville, Victoria, Australia) consists of wrapping the bitten extremity with a bandage and then splinting the limb.25 The “Monash method” (Monash University, Melbourne, Australia) places a firm cloth pad directly over the bite site and then firmly secures it with cloth strips to apply direct pressure.26 The third method is the placement of a full-limb air splint that is then inflated.27 These devices have been evaluated in human studies with radiolabeled mock venoms and in animal studies with radiolabeled venoms from Russell viper (Daboia russelli) and the tiger snake (Notechis scutatus).25-30 In these studies, venom assays rather than clinical parameters were measured. Both the Commonwealth Serum Laboratories and Monash methods have been effective in retarding systemic spread of real and mock venoms in studies,9-14 but the air splint has not been evaluated in this manner.

Some sources in the United States advocate using pressure-immobilization in the early management of coral snake envenomation.31-33 The pressure-immobilization technique has not been formally evaluated in coral snake envenomations.34 We tested the hypothesis that one of these methods, the Commonwealth Serum Laboratories method, would delay the onset of clinical systemic toxicity in a porcine model of M fulvius envenomation.

MATERIALS AND METHODS

A randomized, unblinded, controlled trial of pressure-immobilization bandages in a porcine model of M fulvius envenomation was undertaken. A porcine model was chosen by considerations of availability, cost, acceptability to the institutional animal review committee for experimental study, the expectation that venom toxicity is similar to that seen in humans, and literature supporting its use.35-38 The university animal care use committee approved the study. Subjects were 12 pigs ranging from 9.1 kg to 11.4 kg. Subjects were initially sedated with intramuscular tiletamine (5 mg/kg) and zolazepam (5 mg/kg), intubated, and then kept anesthetized with isoflurane titrated between 1% and 3%. A mixture of nitrous oxide (65%) and oxygen (35%) was also used. Animal care technicians titrated anesthesia to ensure both animal comfort and spontaneous respirations.

Lyophilized M fulvius venom (Natural Toxins Research Center, Kingsville, TX) was resuspended in pure water to a concentration of 10 mg/mL. This venom was obtained from Florida snakes, but no further geographic data are available. With a 27-gauge needle, pigs were injected with 10 mg of venom at a depth of 3 mm (near maximum length of adult M fulvius fangs) in the subcutaneous tissue of the left distal foreleg. Injection site was midway between the distal and middle intraphalangeal joints. Before injection, negative pressure was applied to the syringe plunger to avoid intravascular injection.

The dose of 10 mg was chosen empirically to be lethal in the subjects, given that the lethal adult human dose is 4 to 5 mg.39 A large M fulvius can yield more than 20 mg of venom in a single milking.40,41 All animals received the same dose. The dose was approximately 1 mg/kg and reliably produced fatal respiratory failure within 200 minutes.

After injection, subjects were randomized to either no treatment or a pressure-immobilization bandage 1 minute after envenomation. A forced randomization was accomplished by blindly drawing a card labeled to treat or not to treat. Six cards were labeled “to treat” and 6 “not to treat.” A commercially available 2-inch-wide elastic bandage (Ace wrap) was applied to treated animals by a single operator, beginning at the envenomation site, and then wrapped circumferentially, proceeding proximally to the shoulder. The bandage was applied “as tightly as one would wrap an acute sprain,” which is how many authorities describe field placement of this device.40 Each bandage was checked hourly to ensure that a finger could be easily passed under; none required loosening. Aluminum and foam splints were then loosely taped on either side to immobilize the extremity (Figure 1).

Pulse rate, respiratory rate, pulse oximetry, and quality of respirations were recorded before envenomation and at subsequent 10-minute intervals. The endpoint was either the onset of toxicity in the form of obvious respiratory distress or survival to 8 hours. Respiratory distress was defined as a sustained, nonreversing change in the respiratory pattern marked by bradypnea, an apneic episode, agonal respirations, or falling oxygen saturation. When any of these signs was observed, the animal was checked to ensure proper endotracheal tube placement and patency. Anesthesia was lightened to watch for possible recovery. The pig was then observed until it was clear that severe, irreversible systemic toxicity was occurring, at which point the animal was killed with pentobarbital per institutional protocol. The time to the first observation of sustained respiratory compromise was recorded. As a safeguard, when an
animal did experience respiratory difficulty, the isoflurane was turned off, and the endotracheal tube was checked for placement and patency. Animals that survived to 480 minutes without evidence of severe systemic toxicity were killed. A veterinary pathologist performed necropsies on all subjects.

Statistical analysis was performed using $\chi^2$ analysis and analysis of variance as appropriate.

RESULTS

Two of the subjects, 1 from each group, developed fulminant sanguinous bronchorrhea before the onset of respiratory paralysis. Necropsy verified preexisting pulmonary infections in these 2 animals, so they were removed from the study. None of the 10 remaining pigs demonstrated this finding or had pulmonary abnormalities on necropsy.

Results for individual animals are given in the Table. Four of 5 subjects in the treatment group survived to 8 hours, but none in the control group did ($P=.0036$ using Fisher exact test for categoric data). For the treatment group, the mean time to death was 450 minutes (95% confidence interval [CI] 366.71 to 533.29 minutes; median 480 minutes; interquartile range [IQR] 37.5). For the control group, mean time to death was 182 minutes (95% CI 148.35 to 236.45 minutes; median 182 minutes; IQR 70). For the difference of the mean time to death, the 95% CI was 179.34 to 335.86 minutes. The control animals developed severe toxicity at a mean time of 170±33 minutes, and none survived more than 200 minutes. The one animal in the treatment group who did not survive the 8-hour period of investigation developed respiratory difficulty at 310 minutes. When the statistical analysis was repeated including the 2 animals who died of hemorrhagic bronchorrhea not related to coral snake envenomation, with 4 of 6 animals in the treatment group surviving to 8 hours and 0 of 6 animals in the control group surviving to 8 hours, the $P$ value was .06 (using Fisher exact test for categoric data). Effects of body weight on the time to onset of toxicity was analyzed and found not to be a factor.

Mean values for respiratory rate, oxygen saturation, and pulse rate over time are shown in Figures 2A, 2B, and 2C, respectively. Respiratory rate predictably decreased as animals became toxic, and pulse rate correspondingly increased. Oxygen saturation decreased rapidly when subjects became severely toxic, but this was a late finding and a sign of imminent respiratory failure. All endotracheal tubes were found to be functioning properly at the endpoints, and no subject recovered in the absence of isoflurane.

At death, the bandages were removed, and all animals were subject to necropsy by a veterinary pathologist. Histologic examination revealed no evidence of pressure or ischemic-induced injury at any of the envenomation sites. Minor localized hemorrhage was observed in all envenomation sites, possibly because of venom effects.

LIMITATIONS

This study has several limitations. Investigators were not blinded to which subjects received a pressure-immobilization dressing. A relatively small number of animals were used. Animals were of necessity anesthetized and received supplemental oxygen. Animals were not prescreened for respiratory pathology, which led to 2 pigs being removed from the study.
The alternative interpretation, that the pressure-immobilization bandage failed in the pigs in the treatment group that developed hemorrhagic bronchorrhea, is inconsistent with the known effects of coral snake venom. Measurements of venom levels were not performed and, if available, would have been helpful in confirming results. This study applied pressure-immobilization bandages under “field conditions,” in that we did not measure bandage pressures. The pressure-immobilization bandage was applied 1 minute after the injection of venom, and this rapidity most likely will not be duplicated in the field.

The animals received supplemental oxygen mixed with the isoflurane through the ventilator circuit because this was the only way to deliver the anesthetic with the equipment available. We would have preferred room air as the dissolving gas because the increased oxygen concentration could theoretically prolong survival. All subjects received the same mixture.

**DISCUSSION**

This study is the first to evaluate pressure-immobilization bandage efficacy in coral snake envenomation. Speculation and controversy over the usefulness of these devices in coral snake envenomations is found in the current emergency medicine, wilderness medicine, and toxicology literature. Most references mention that this technique could be useful but that it has not been formally studied. Some references state that the technique is not useful despite the previous lack of research. These sources state that coral snake venom is absorbed by the venous system as opposed to the lymphatics, which is unlikely, considering the snake’s very small fangs (1 to 3 mm), unsophisticated venom delivery system, and the minute quantities of venom injected. If coral snake venom were hematogenously spread, victims would become systemically toxic rapidly, when in fact the hallmark of coral snake envenomations is a period of delay of up to 12 hours to the onset of systemic symptoms. In most snake envenomations, coral included, venom is deposited in the subcutaneous tissue, where it is transported proximally by the lymphatics.

The onset of toxicity was sudden and dramatic in all cases. After injection, most subjects experienced tremors in the affected limb, which appeared to progress to full-limb jerks and apparent involuntary movements. Several appeared to have fasciculations. These movements would persist for several minutes and then subside. These observations were much more apparent in the control animals, although the range of motion was restricted in the splinted animals. After the movements ceased, there was a period during which the animals were asymptomatic, with normal respiratory patterns. At a mean time of 170±33 minutes, control pigs developed signs of systemic toxicity that progressed to fatal respiratory distress.

The earliest sign of systemic poisoning was a noticeable change in the respiratory mechanics of the animals. The pigs appeared to have more shallow respirations with increased reliance on abdominal musculature. Respiratory rate would then decrease. Two of the control pigs experienced apneic episodes as the first sign of severe toxicity, and the other 3 went from respiring normally to agonal respirations within a 10-minute period.

A significant challenge of the study was how to keep the subjects anesthetized and immobile and breathing spontaneously without compromising respiratory status. In consultation with veterinary experts and animal care technicians, we chose to initially sedate the animals with a single intramuscular injection of tiletamine and zolazepam and then maintain anesthesia with isoflurane, which has minimal respiratory effects at usual doses. The agents worked well, and none of the animals experienced respiratory depression before envenomation. The animal care technicians and veterinarian witnessed the respiratory changes and did not think they were consistent with isoflurane effects.

One of the 5 treated animals exhibited severe toxicity and died at 310 minutes, which could have occurred for several reasons. Injection error could have placed venom in or very near a blood vessel, although precautions were taken to avoid this. An intravascular injection would result in death despite placement of the bandage because arterial and deep venous flows are preserved. Bandaging error is another possibility; if the bandage was placed too loosely, it may have been ineffective, although bandages were standardized as described. Finally, it must be considered that pressure-immobilization bandages are not perfect and have failures.

On the basis of the results of the study, we propose that pressure-immobilization be considered in the management of coral snake envenomations until definitive care is available to the patient. The device proved to be protective against systemic
venom toxicity and more than doubled average survival time. The pressure-immobilization technique is simple, uses common materials, and should be taught to out-of-hospital providers and medical personnel in areas where coral snakes are endemic. With remaining stocks of North American coral snake antivenom in short supply and no immediate alternative, delaying toxicity will be essential in reducing the morbidity and mortality resulting from these envenomations. Use of pressure-immobilization devices should be also considered in Latin American countries, where snakes bites are more frequent and access to medical care is often delayed.

We thank the veterinarians and staff at the Comparative Medicine Center at East Carolina University for their help and support. John Bradfield, DVM, PhD, Kenneth Salleng, DVM, and Dale Aycock, AAS, LATG, provided exceptional assistance.

Author contributions: BTG, KB, JBH, and WJM were involved in the design of the study, working in the laboratory, and preparation of the manuscript. BTG, WJM, and KB were involved in ordering materials. KB was involved in the statistical analysis. WJM takes responsibility for the paper as a whole.

Funding and support: This study was funded by the Emergency Medicine Residents Research Fund at the Brody School of Medicine Medical Foundation.


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REFERENCES


