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# Crotalidae Polyvalent Immune Fab (Ovine) Antivenom Is Efficacious for Envenomations by Southern Pacific Rattlesnakes (*Crotalus helleri*)

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**Study objective:** Southern Pacific rattlesnake (*Crotalus helleri*) venom is not 1 of the 4 venoms used to produce Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV). There is currently no published clinical experience regarding the efficacy of this new antivenom for confirmed *C helleri* envenomation, and animal data suggest greatly diminished efficacy. We assessed the efficacy of FabAV for patients with confirmed *C helleri* envenomation.

**Methods:** We conducted a prospective observational study of 23 consecutive rattlesnake envenomations that were treated with FabAV at our center. Patients were excluded if the species of snake could not be confirmed, if FabAV antivenom was not given, or if Antivenin (Crotalidae) polyvalent (equine) was given. We collected serial physical examination and laboratory data over a 24-hour period to serially evaluate the severity score and performed follow-up to evaluate delayed reactions.

**Results:** There were 15 patients who received FabAV and had the species of rattlesnake confirmed (9 *C helleri*, 4 *C scutulatus scutulatus*, 1 *C mitchellii pyrrhus*, 1 *C ruber ruber*). *C helleri* envenomations demonstrated similar improvement in serial snakebite severity scores to those of other species. Three patients treated with scheduled dosing had recurrence of progressive swelling (2 *C helleri* and 1 *C mitchellii pyrrhus*) during the 24-hour study period.

**Conclusion:** We observed similar improvement in FabAV-treated patients with *C helleri* envenomation compared with those of other species and conclude that this treatment in standard doses appears efficacious for bites by this species. Progressive swelling may recur despite scheduled dosing.

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## INTRODUCTION

Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV) is a new antivenom for treating pit viper envenomation. According to the manufacturer, FabAV is indicated for envenomations by all "North American crotalid" species,[1] which includes rattlesnakes (genera *Crotalus* and *Sistrurus*), as well as cottonmouths and copperheads (genus *Agkistrodon*). However, the FabAV production process uses the venoms of only 4 species: western diamondback rattlesnake (*C atrox*), eastern diamondback rattlesnake (*C adamanteus*), Mojave rattlesnake (*C scutulatus scutulatus*), and cottonmouth or water moccasin (*A piscivorus*).

Envenomations by Southern Pacific rattlesnakes (*C helleri*, formerly *C viridis helleri*)[2] are among the most common snakebites presenting to our center. The range of this species includes a densely populated portion of the United States. Venom from *C helleri* is not used to produce FabAV. A murine lethality study revealed that this antivenom demonstrated relatively good cross-protection against venoms not used in the immunization of flocks used to produce it, except for *C helleri*, in which a very high dose was required to provide the same level of protection.[3] The manufacturer discloses that FabAV may not be efficacious for this species of rattlesnake.[1] In contrast, FabAV appears effective for *C scutulatus scutulatus* envenomation.[3,4] The venom A type of *C scutulatus scutulatus* venom ranks among the most lethal of North American snake venoms.[5] However, in the animal model, more than 100 times as much FabAV was required to prevent lethality from *C helleri* venom as was required for *C scutulatus scutulatus* venom A.[3] To our knowledge, there is currently no published clinical experience using FabAV for confirmed *C helleri* envenomation. Our objective was to assess the efficacy of FabAV for bites by *C helleri*.

## MATERIALS AND METHODS

We enrolled consecutive patients of any age examined at our center after rattlesnake bites during the period from April 2001 through September 2001. We excluded patients to whom FabAV was not administered, patients to whom Antivenin (Crotalidae) polyvalent (equine) was administered, and cases in which snake identification was inconclusive. Quality photographs of each snake were reviewed independently by 3 study coauthors, each an experienced herpetologist skilled at crotaline identification (one a PhD herpetologist). The institutional review board at our medical center approved this study.

The decision to treat a patient was made by the treating physician in conjunction with an envenomation specialist, and the protocol for treatment was based on recommendations in the FabAV package insert.

After obtaining written informed consent, investigators collected serial physical examination and laboratory data (including coagulation parameters, platelet count, and fibrinogen) using a standardized data collection tool. All data collection was performed by the principal investigator or by a resident physician directly supervised by the principal investigator. Each patient's clinical condition was evaluated and recorded at presentation, at 1 hour after the initial dose(s) of FabAV, and at 6, 12, 18, and 24 hours after initial control was achieved. Laboratory parameters were assessed at presentation and at 1 hour after each infusion of FabAV.

"Initial control" was defined as the arrest of progression for at least 6 hours of any and all components of the envenomation syndrome (ie, no further advancement of swelling, resolution of systemic effects, and improving coagulopathy). Swelling was measured from the most distal fang mark to the edge of advancing edema. After initial control was achieved, additional antivenom was given in accordance with recommendations in the package insert if the treating physician and envenomation specialist judged it to be indicated.

We defined "local recurrence" as the return of new progressive circumferential swelling after initial control.[6,7] That is, the leading edge of edema begins to advance from distal to proximal again. At each time interval for each patient, we calculated the snakebite severity score, a validated quantification of envenomation based on limb swelling, coagulation tests, and neu-

rologic, cardiovascular, pulmonary, and gastrointestinal symptoms and/or signs.[8] "Efficacy" was defined as a decrease or no change in severity score.[9]

Acute adverse reactions to FabAV were documented. Patients were followed up at 21 days or more after treatment to evaluate for delayed hypersensitivity reactions.

We used descriptive statistics to report our results.

It should be noted that, although taxonomy has changed, the family name *Crotalidae* is used in the product name and "crotalid" is used in the package insert. Pit vipers were formerly classified as a distinct family named *Crotalidae*, but are now recognized as subfamily *Crotalinae* within the family *Viperidae*.[10]

## RESULTS

We evaluated all 23 patients with snakebites who presented to our medical center during the study period. Four cases were excluded because Antivenin (Crotalidae) polyvalent (equine) had been administered and another 4 were excluded because the snake species could not be conclusively identified. This left 15 patients for the study, including 9 bitten by *C helleri*, 4 by *C scutulatus scutulatus*, 1 by *C mitchellii pyrrhus* (southwestern speckled rattlesnake), and 1 by *C ruber ruber* (red diamond rattlesnake). Snake identification was unanimous in all 15 cases.

Serial snakebite severity scores declined over time in all species (Table). A comparison of snakebite severity scores for *C helleri* and *C scutulatus scutulatus* is graphically illustrated in the Figure. The 4 patients excluded for inconclusive identification appeared to have a similar response to the antivenom.

Initial control of the envenomation syndrome after bites by *C helleri* was obtainable in our patients after 6 to 12 vials of FabAV (mean±SD dose 7.2±3.5 vials). The

**Table.**
*Snakebite severity scores after bites by formally identified rattlesnakes and treatment with FabAV.*

| Patient No. | Species | Dose to Achieve Initial Control | Subsequent Dosing | Snakebite Severity Score | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Presenting | After Initial Control | At 6 h | At 12 h | At 18 h | At 24 h |
| 1 | *C helleri* | 6 vials | None | 6 | 4 | 4 | 3 | 3 | 3 |
| 2 | *C helleri* | 12 vials | 2 vials every 6 h for 3 doses | 6 | 3 | 3 | 2 | 2 | 2 |
| 3 | *C helleri* | 6 vials | 2 vials every 3 h for 3 doses | 3 | 2 | 2 | 2 | 2 | 2 |
| 4 | *C helleri* | 6 vials | 2 vials every 6 h for 3 doses | 3 | 3 | 3 | 3 | 2 | 2 |
| 5 | *C helleri* | 12 vials | 2 vials every 6 h for 3 doses | 5 | 5 | 5 | 4 | 3 | 3 |
| 6 | *C helleri* | 6 vials | 2 vials every 6 h for 3 doses | 2 | 2 | 2 | 2 | 2 | 2 |
| 7 | *C helleri* | 10 vials | 2 vials every 6 h for 3 doses | 4 | 2 | 2 | 3* | 3 | 3 |
| 8 | *C helleri* | Approximately 1 vial | None | 2 | NA | 1 | 1 | 1 | 0 |
| 9 | *C helleri* | 6 vials | 2 vials every 6 h for 5 doses | 4 | 3 | 3 | 4* | 3 | 3 |
| 10 | *C scutulatus scutulatus* | 6 vials | 2 vials every 6 h for 3 doses | 6 | 4 | 4 | 4 | 2 | 2 |
| 11 | *C scutulatus scutulatus* | 6 vials | 2 vials every 6 h for 3 doses | 4 | 4 | 2 | 1 | 1 | 1 |
| 12 | *C scutulatus scutulatus* | 6 vials | None | 1 | 0 | 0 | 0 | 0 | 0 |
| 13 | *C scutulatus scutulatus* | 6 vials | 2 vials every 6 h for 3 doses | 9 | 2 | 1 | 1 | 1 | 1 |
| 14 | *C mitchellii pyrrhus* | 6 vials | 2 vials every 6 h for 3 doses† | 7 | 2 | 2 | 3* | 3 | 3 |
| 15 | *C ruber ruber* | 6 vials | 2 vials every 6 h for 3 doses‡ | 6 | 5 | 4 | 4 | 1 | 1 |
| **Summary data§** | | | | | | | | | |
| | *C helleri* | 12.3±1.9 vials total (range 1–18) | | 4 (3–5) | — | 3 (2–3) | 3 (2–3) | 2 (2–3) | 2 (2–3) |
| | *C scutulatus scutulatus* | 10.5±1.5 vials total (range 6–12) | | 5 (2.5–7.5) | — | 1.5 (0.5–3) | 1 (0.5–2.5) | 1 (0.5–1.5) | 1 (0.5–1.5) |

**NA,** Not applicable.
*Local recurrence.
†Six additional vials were given at 18 hours.
‡Four additional vials were given at 12 hours.
§Reported as mean±SD for vials and median (interquartile range) for snakebite severity score.

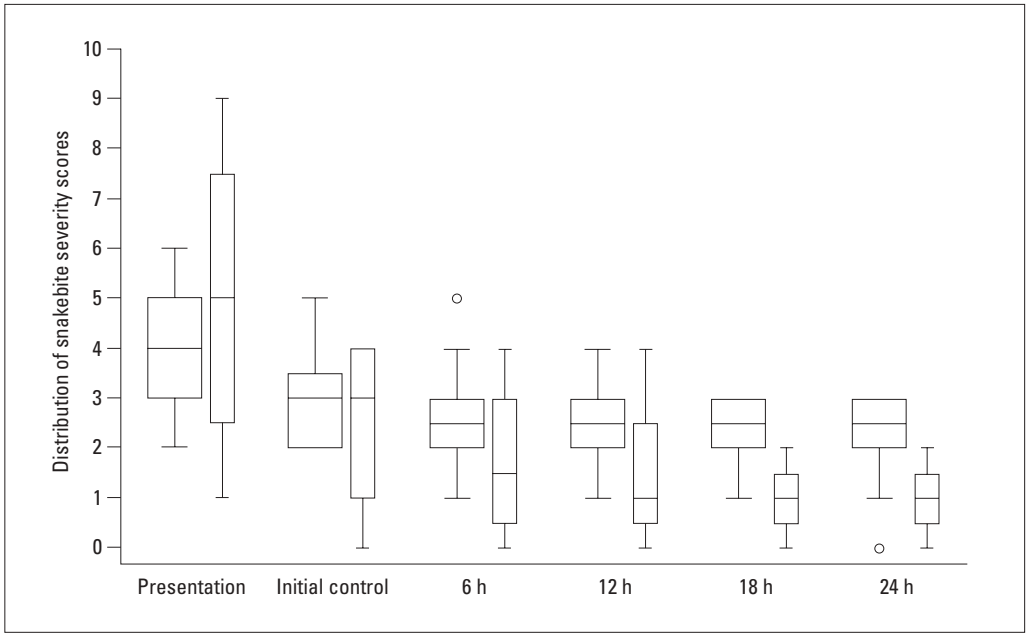
severity score improved or remained the same for at least 6 hours in all 15 patients. The severity score for 12 patients continued to improve or remained the same during the rest of the 24-hour study period; however, 3 patients experienced local recurrence despite 2-vial maintenance doses at 6, 12, and 18 hours. In each case, progressive swelling returned sometime between scheduled measurements at 6 and 12 hours. In patient 7, the advancing edge of edema began at 18 cm from the bite site and progressed to 40 cm. In patient 9, swelling progressed from 33 to 38 cm. In patient 14, swelling progressed from 23 to 56 cm. In each case, recurrent swelling was associated with pain and tenderness in the involved areas, but was not associated with other local or systemic symptoms or signs. Additional antivenom was administered to these 3 patients at scheduled dosing intervals (Table).

Systemic effects (eg, hypotension, vomiting, neurologic effects) occurred in several patients. Patients 13 and 14 had hypotension and severe tachycardia. Patients 2, 4, 11, and 13 had nausea, vomiting, or both. Patient 2 had fasciculations remote from the bite site. Patients 2, 10, and 13 had generalized weakness and difficulty breathing. Patient 13 was also lethargic. Ten patients had paresthesias. It is possible that additional patients had paresthesias; however, we were unable to elicit this history from young patients. Systemic effects improved promptly with FabAV administration. No patients had recurrence of systemic effects.

Other than oozing from fang puncture wounds and ecchymosis around the bite site, no patient in our series had bleeding complications. Only patient 15 developed coagulopathy (fibrinogen <20 mg/dL and international normalized ratio >3.0), which improved after FabAV was administered.

Patient 2 developed a faint macular, mildly pruritic rash on the abdomen and left thigh 10 minutes into the initial infusion of FabAV. This resolved promptly after intravenous administration of 50 mg of diphenhydramine and 300 mg of cimetidine. The reaction did not recur despite continuation of the FabAV infusion. Patient 8, who had a known history of myocardial infarction with stable angina, developed chest pain, nausea, and diaphoresis after 50 mL of an infusion of 6 vials of FabAV (which had been diluted into a total volume of 250 mL). He did not develop symptoms or signs of acute hypersensitivity (ie, there was no urticaria or wheezing). However, the infusion was stopped, and the

**Figure.**
*Improvement in snakebite severity scores. The line in the middle of each boxplot represents the median or 50th percentile of the data. The box extends from the 25th percentile to the 75th percentile, and the lines extend to the 5th and 95th percentiles. Outlier points are shown as circles.* C helleri *is signified by wide boxplots (n=9);* C scutulatus scutulatus *is signified by narrow boxplots (n=4).*



patient's symptoms resolved with 0.4 mg of sublingual nitroglycerin and 0.625 mg of intravenous droperidol. The patient became mildly hypotensive after nitroglycerin, but this resolved within 5 minutes after a 250-mL bolus of normal saline solution. No more antivenom was given because the patient had no further progression of swelling and no systemic effects, and laboratory studies were normal.

On follow-up, patient 3 reported that, 31 days after treatment with FabAV, he developed mild urticaria with exertion that lasted about an hour and resolved completely with rest. Medical care was not sought, and the patient took no medication. No other patients reported adverse reactions after hospital discharge on follow-up at least 21 days after treatment.

## DISCUSSION

To our knowledge, this is the first report of the use of FabAV for confirmed *C helleri* envenomation. Furthermore, our study corroborates previous reports from an animal study[3] and a single case report[4] showing FabAV to be efficacious for envenomations by *C scutulatus scutulatus*. Our study is the first documented experience in human beings or animals using this new antivenom for *C mitchellii pyrrhus* and *C ruber ruber* envenomation (these venoms are not used to produce FabAV).

The antivenom dose used in our series (7.2±3.5; mean±SD) to achieve initial control of the envenomation syndrome is similar to the dose (7.8±3.0; mean±SD) used in a recently reported series. Although species were not identified in that series, nearly all of the bites originated outside of the geographic range of *C helleri*.[6] Likewise, the changes in severity scores from presentation to 6 and 12 hours after treatment for our series of patients with *C helleri* envenomations were also similar to the changes reported in 2 other studies from areas outside the geographic range of *C helleri*.[6,9] In these 2 series, the severity scores at presentation were 4.4±1.9 (mean±SD) and 3.9±2.2 (mean±SD), and at 12 hours they were 2.4±1.2 and 2.6±1.0 (mean±SD).[6,9] These values are very similar to the scores in our series of patients with *C helleri* bites (Table). Although not a formal comparison, we infer that the efficacy of FabAV for bites by *C helleri* is approximately equivalent to its efficacy for envenomations by other species of rattlesnakes.

FabAV appears as effective for *C helleri* bites as for *C scutulatus scutulatus* bites up through 6 hours (Figure). After this time, however, there seems to be no further improvement in *C helleri* scores, in contrast with *C scutulatus scutulatus* scores. This apparent difference in efficacy might be expected because FabAV is made using *C scutulatus scutulatus* venom, but not *C helleri* venom. Because the initial response of the 2 species is similar, however, another possible explanation is that envenomation by *C scutulatus scutulatus* from our region produced predominantly systemic effects (ie, neurologic) without injuring tissue around the bite site, whereas *C helleri* venom effects are generally more tissue destructive. In our series, neurologic effects (eg, weakness, paresthesias, fasciculations) and other systemic effects (eg, hypotension, tachycardia, vomiting) were most manifest at presentation. These effects resolved relatively quickly after antivenom and other resuscitative measures. In contrast, although progression of swelling ceased after treatment, it did not rapidly reverse. Other manifestations of injury around the bite site (eg, venom-digested tissue, ecchymosis, bullae) required comparatively much more time to heal. Therefore, the differences in severity scores after 6 hours may be explained by the observation that systemic effects associated with either species resolved relatively quickly, whereas injury to local tissue, more often associated with *C helleri* envenomation, improved more slowly. This subtle difference starkly contrasts with the 100-fold difference in efficacy observed in the animal study.[3]

Two vials of FabAV administered every 6 hours for 3 doses (per package insert recommendations) did not prevent local recurrence in 3 patients from our series. In contrast, Dart et al[6] did not note local recurrence in any of their 15 patients given scheduled dosing. Although local recurrence was observed in our series despite scheduled dosing of FabAV in 2 patients with *C helleri* envenomations, it was also observed in a patient with a *C mitchellii pyrrhus* envenomation. In another series

from a center outside the range of *C helleri*, it was similarly noted that swelling can progress after initial control despite scheduled dosing of FabAV.[11]

Recurrence phenomena are thought to occur because free (unbound) Fab fragments clear faster than venom components.[12] Because development of local recurrence despite scheduled dosing of FabAV is not unique to *C helleri* envenomation, the recurrence was probably not related to differences in efficacy among snake species whose venoms are not used to make FabAV. Although local recurrence was not observed after *C scutulatus scutulatus* envenomations in our series, it is likely that this was related to differences in the envenomation syndromes after bites by *C scutulatus scutulatus* from our area (ie, more neurologic symptoms and less swelling). Recurrence may primarily be a phenomenon associated with the pharmacokinetic/pharmacodynamic properties of the antivenom.

Although scheduled dosing may reduce the chance that local recurrence may develop, it does not completely prevent it. The exact time of the onset of recurrent progressive swelling is not known. Until more clinical experience is gained with this new antivenom and optimal dosing is better understood, patients with snakebites treated with FabAV require very close observation and frequent measurements (eg, every 1 to 2 hours) of swelling for at least 24 hours. We believe that additional FabAV should be given as soon as progressive swelling recurs and should continue until control is subsequently regained.

Author contributions: SPB conceived and designed the study, supervised the conduct of the study, coordinated data collection, undertook recruitment of patients, managed the data (including quality control), and drafted the manuscript. JAM collected data for 3 cases included in this series. SPB, SMG, and WKH analyzed the data. SPB, WKH, and MDC confirmed all of the snakes' species. All authors contributed substantially to the revision of the manuscript before submission. SPB takes overall responsibility for the paper as a whole.

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