Randomized Controlled Trial of Intravenous Antivenom Versus Placebo for Latrodectism: The Second Redback Antivenom Evaluation (RAVE-II) Study

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Study objective: Latrodectism is the most important spider envenomation syndrome worldwide. There remains considerable controversy over antivenom treatment. We aimed to investigate whether antivenom resulted in resolution of pain and systemic effects in patients with latrodectism who received standardized analgesia.

Methods: In a multicenter randomized placebo-controlled trial of redback spider antivenom for latrodectism, 224 patients (>7 years) with a redback spider bite and severe pain, with or without systemic effects, were randomized to receive normal saline solution (placebo) or antivenom after receiving standardized analgesia. The primary outcome was a clinically significant reduction in pain 2 hours after trial medication compared with baseline. A second primary outcome for the subgroup with systemic features of envenomation was resolution of systemic features at 2 hours. Secondary outcomes were improved pain at 4 and 24 hours, resolution of systemic features at 4 hours, administration of opioid analgesics or unblinded antivenom after 2 hours, and adverse reactions.

Results: Two hours after treatment, 26 of 112 patients (23%) from the placebo arm had a clinically significant improvement in pain versus 38 of 112 (34%) from the antivenom arm (difference in favor of antivenom 10.7%; 95% confidence interval −1.1% to 22.6%; P=.10). Systemic effects resolved after 2 hours in 9 of 41 patients (22%) in the placebo arm and 9 of 35 (26%) in the antivenom arm (difference 3.8%; 95% confidence interval −15% to 23%; P=.79). There was no significant difference in any secondary outcome between antivenom and placebo. Acute systemic hypersensitivity reactions occurred in 4 of 112 patients (3.6%) receiving antivenom.

Conclusion: The addition of antivenom to standardized analgesia in patients with latrodectism did not significantly improve pain or systemic effects. [Ann Emerg Med. 2014;64:620-628.]

Please see page 621 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Spider bite is a common problem worldwide.[1] Latrodectism is the most common severe spider envenoming syndrome and is caused by widow spider (*Latrodectus* spp) bites, particularly in warmer parts of America, Europe, and Australia.[2-4] In Australia, there are 3,000 to 5,000 cases every year.[3] Widow spiders are medium-sized black spiders that vary in appearance and include 30 species on most continents.[5] Envenoming is characterized by local, regional, or generalized pain associated with systemic symptoms and autonomic effects. The severity and features of latrodectism appear to vary for different widow spiders from different regions,[2-4,6-9] but pain is the most prominent feature in all cases.

Despite the medical importance of latrodectism, treatment continues to be problematic, with wide variations in clinical practice worldwide.[1] Antivenom is available only in some countries,[10] and there is controversy about its effectiveness and safety.[1] In the United States, there has been limited use of antivenom because of the perceived risks of adverse reactions after a death attributed to antivenom.[4] In Australia, a highly purified equine antivenom raised against the local species *L hasselti* (redback spider) has been widely used for 60 years, mainly by the intramuscular route. Its introduction was before the era of randomized controlled clinical trials. Numerous other treatments with little evidence for effectiveness have been used, including benzodiazepines, calcium, magnesium, and combinations of nonopioid and opioid oral analgesia.[1]

Three randomized controlled trials of antivenom for latrodectism have been published.[2,11,12] Two previous trials in

Editor's Capsule Summary

What is already known on this topic

Latrodectus (widow) spider envenomation can cause severe pain but is rarely fatal.

What question this study addressed

Does antivenom reduce pain and systemic effects (eg, abdominal pain) after a redback widow spider (*Latrodectus hasselti*) bite?

What this study adds to our knowledge

In this 224-patient, randomized, placebo-controlled, adequately powered, Australian clinical trial, antivenom did not produce a clinically meaningful reduction in pain severity or systemic effects.

How this is relevant to clinical practice

Redback spider antivenom does not appear beneficial for widow spider envenomation.

Australia both reported no difference between intravenous and intramuscular antivenom.[2,11] These were unexpected outcomes because it was assumed that intravenous antivenom would be more effective. In addition, a pharmacokinetic analysis of a subgroup of patients from one trial found that antivenom was detectable in serum only after intravenous administration.[13] A small phase II study of black widow spider antivenom versus placebo found no significant benefit of antivenom over placebo.[12] Taken together, these results suggested that antivenom might be no more effective than placebo and provided sufficient doubt to warrant a placebo-controlled trial.

The aim of this study was therefore to determine whether the administration of redback spider antivenom is superior to placebo for treating the pain and systemic effects of latrodectism in patients already receiving standardized analgesic treatment.

MATERIALS AND METHODS

This was a placebo-randomized controlled trial of redback spider antivenom in patients with moderate to severe latrodectism (redback spider envenoming), with a primary outcome of a clinically significant reduction in pain 2 hours after the trial medication (compared with baseline). A second primary outcome for the subgroup with systemic features of envenoming was the resolution of these features also at 2 hours. Two primary endpoints were chosen because both types of response are clinically important but not necessarily linked. All participants received analgesia according to a standardized protocol, commenced before the administration of trial drug or placebo. The study was approved by 7 human research ethics committees to cover all hospital sites. The trial was registered with the Australian New Zealand Clinical Trials Registry, http://www.anzctr.org.au/, ACTRN12609000063213.

Selection of Participants

Patients were recruited from 20 emergency departments (EDs) around Australia between January 2009 and June 2013 if they had a redback spider bite and the treating clinician would normally administer antivenom or analgesia for the pain, or systemic envenoming. A redback spider bite was defined as either a bite by a spider that was clearly identified as a redback spider (by the patient or clinician) or a clinical syndrome consistent with typical redback spider envenoming, that is, the sensation of a bite followed by 2 or more of the following: increasing pain during the first hour, radiating, regional, or generalized pain, and local or regional diaphoresis.

Local envenoming was defined as severe local pain, for which the patient was requesting analgesia, or that was preventing sleep. Systemic envenoming was defined as the presence of greater than or equal to 3 of the following: nausea, vomiting, headache, lethargy, malaise, and abdominal pain.

Exclusion criteria were aged younger than 8 years (because of the unreliability of the Verbal Numerical Rating Scale for assessment of pain in this group), prior administration of antivenom and presentation to the hospital more than 36 hours after the bite.

Patients were identified by nursing or medical staff on or soon after admission. It was not possible to keep a record of patients with redback spider bites not recruited to the study because the investigators were contacted only for patients who met the inclusion criteria. The study was explained and written informed consent was obtained from the patient or the parent or guardian of the patient. The treating physician then contacted a national toll-free telephone number to enroll the patient and receive a randomization code. The patient was put in an acute observation area with cardiac monitoring, pulse oximetry, and automated blood pressure measurements, and an intravenous cannula was inserted.

All patients received a standard analgesia protocol before receiving the study intervention with oral paracetamol 1 g (20 mg/kg up to a maximum of 1 g in children), ibuprofen 800 mg (10 mg/kg up to a maximum of 800 mg in children), and oxycodone 5 mg (0.1 mg/kg up to a maximum of 5 mg in children).

The Calvary Mater Newcastle pharmacy in conjunction with Richard Stenlake Compounding Chemist (Sydney, New South Wales, Australia) produced prepacked kits for the trial. Each treatment kit contained 2 vials of either redback spider antivenom or normal saline solution. Normal redback spider antivenom vials (equine Fab′2 antivenom, 500 U/vial, raised against *L hasselti*), as well as identical empty vials, were purchased from CSL Ltd (Parkville, Victoria, Australia). The compounding chemist filled the identical (empty) vials with normal saline solution, which was visually indistinguishable from antivenom. Labels were removed from vials and the central pharmacy relabeled the vials with study numbers. Each kit was then

randomized to contain either 2 vials of antivenom (active) or 2 vials of normal saline solution (placebo).

Block randomization was used (with variable block sizes of 2 and 4), with stratification between local and systemic envenoming. Block sizes of 2 and 4 meant that each pack of 4 randomized treatments provided to the hospital might feasibly contain any combination of placebo and antivenom (including 4 antivenom or 4 placebo), making it impossible to predict the last kit in each pack. During the study, each site was kept stocked with 2 packs each containing 4 treatment kits, one pack of 4 for local envenoming and the other for systemic envenoming.

Using a prerandomized list of blocks, the chief investigators and on-call research assistants allocated study codes to patients in sequential order based on the hospital site and whether the patient had systemic effects or not. The study code was then used to identify the correct trial pack stored at the site. The content of each treatment pack (active or placebo) was known only by the centralized pharmacy so that treating clinicians, patients, and investigators were blind to the study intervention.

The trial drug was administered (2 vials of placebo or 2 vials of redback spider antivenom) mixed in 200 mL normal saline solution during 20 minutes. The patient had continuous monitoring (ECG, pulse oximetry, and noninvasive blood pressure) during the infusion of the study drug and for 30 minutes after completion. Study observations were performed at 2 hours and 4 hours after infusion commencement, and patients remained in the hospital until at least 4 hours after the study drug. Further study observations were conducted immediately before discharge if patients were kept in the hospital for longer than 4 hours.

After measurement of the primary endpoint 2 hours from study commencement, parenteral opioid analgesia (eg, morphine) and (unblinded) doses of redback spider antivenom were permitted and their use was determined by the treating physician. All patients received regular ibuprofen (400 mg 3 times daily) for 24 to 48 hours and oxycodone as required after the 4-hour study period.

Data Collection and Processing

Data collected on case report forms included patient demographics, details of the bite (spider identification and circumstances of the bite), baseline clinical effects, serial clinical effects during the study, additional treatment (analgesia and unblinded redback spider antivenom), and adverse reactions. Pain was assessed with a verbal numeric rating scale that required the patient to verbally provide a score between 0 and 10 inclusive, in which 0 represented "no pain" and 10 "worst pain possible." Immediate-type hypersensitivity reactions were recorded according to a previously published grading scale as skin-only systemic hypersensitivity reactions, anaphylaxis, or severe anaphylaxis (hypotension or hypoxia).[14]

Patients were followed up by telephone by a research assistant at 24 hours from the time of administration of the study treatment, 7 to 10 days, and 6 weeks to assess for effectiveness and adverse events, including symptoms of serum sickness. The research assistant used a pro forma to ask the patient predefined questions, including the Verbal Numerical Rating Scale, whether any further analgesia was used, whether the patient was readmitted to the ED or hospital, or whether the patient visited his or her local physician. In addition, they asked about each of the symptoms of serum sickness at the 7- to 10-day and 6-week follow-up.

Primary Data Analysis

The first primary outcome was a clinically significant reduction in the severity of pain 2 hours after the commencement of the study treatment using the Verbal Numerical Rating Scale. This depended on the baseline starting point: a reduction of 2 or greater was required for baseline score of 0 to 3, 3 or greater for a baseline score of 4 or 5, 4 or greater for a baseline score of 6 or 7, and 5 or greater for a baseline score of 8 to 10. This approach was similar to that previously used in the Redback Antivenom Evaluation I (RAVE I) study (Appendix E1, available online at http://www.annemergmed.com).[2] The required reduction for each baseline score was modified slightly after trial registration but before unblinding of the data because of an inconsistency in the registered method that would have given inconsistent results in patients with similar scores (Appendix E1, available online at http://www.annemergmed.com). The second primary outcome was a resolution of systemic features of envenoming within 2 hours in the subgroup of patients with systemic envenoming. Resolution of systemic envenoming was defined as not having more than 1 remaining systemic symptom or feature. Both primary outcomes were analyzed by intention to treat.

Secondary outcomes were predefined as clinically significant reduction in pain and resolution of systemic features (if present) at 4 hours (same definition of resolution as at 2 hours), administration of opioid analgesics (oral or parenteral) or further doses of antivenom after 2 hours, a clinically significant reduction in pain at 24 hours, use of opioid analgesia after discharge, representations for medical care, acute systemic hypersensitivity reactions, and serum sickness defined as 3 or more characteristic symptoms (fever, malaise, rash, itchiness, myalgia, and arthralgia). Predefined subgroup analyses were planned for patients with systemic envenoming.

A sample size of 240 (including 94 patients with systemic effects) was calculated to give 80% power to detect a 20% difference in the primary outcome of clinically significant pain reduction (regarded to be a clinically important difference by clinicians[15]) or a 30% difference in the primary outcome of resolution of systemic effects. The study was stopped early (16 patients short of the sample size) because there was no further funding to resupply all 20 hospitals with antivenom and placebo trial packs, which expired annually and had to be replaced before the next bite season.

Once the study was finished and all data were entered into the study database, the chief clinical investigator (G.K.I.) remained blinded to the allocation and audited all primary and secondary outcomes against original datasheets and clinical notes. If an inconsistency was identified, a second investigator (S.G.A.B. or

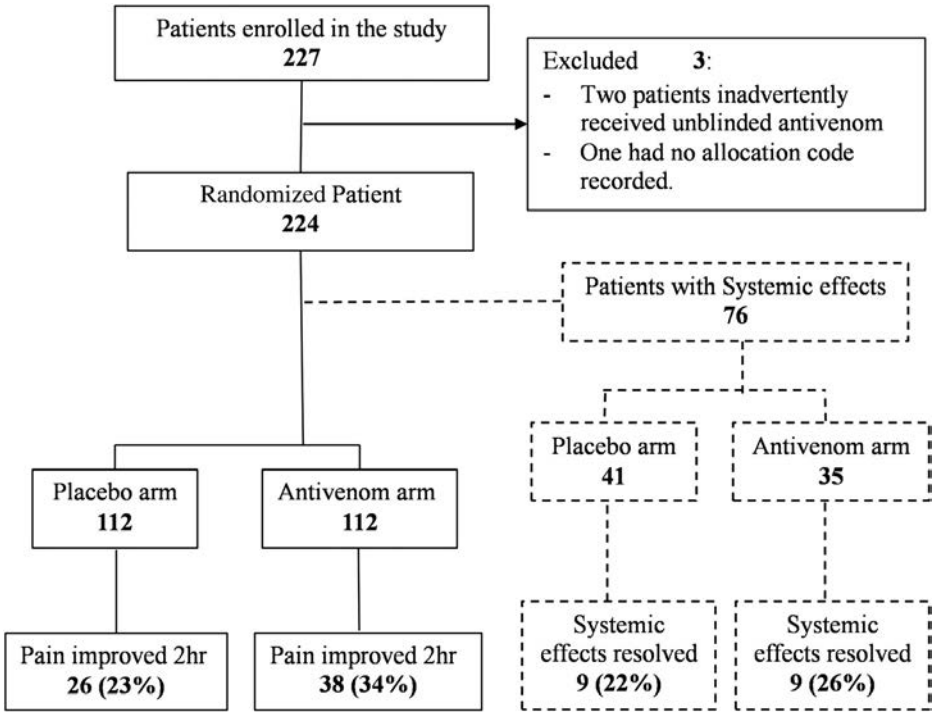

Figure 1. Flow chart of all persons recruited to the study, their allocation to placebo or antivenom, and the 2 primary outcomes.

C.B.P.) adjudicated. During this stage, only the study numbers, not group allocation, were known to these investigators. One investigator not involved with the day-to-day conduct of the study (N.A.B.) was then supplied with the blinded data and separately with the group allocation as either A or B by the central pharmacy. He undertook the study analysis independently and presented this to the writing group. The final analysis was then approved before the central pharmacy revealed whether A or B was antivenom.

Continuous variables were presented as medians with interquartile ranges, and proportions were given with 95% confidence intervals (CIs). Dichotomous primary outcomes were analyzed with a 2-tailed Fisher's exact test ($P<.05$ to be significant). Continuous secondary outcomes were analyzed by either a *t* test (parametric) or Mann-Whitney test (nonparametric). A post hoc analysis was performed with the primary pain outcome as a continuous variable according to percentage pain reduction. This also explored whether there was any effect of time from the bite to antivenom on response in the antivenom arm, using linear regression. All analyses and graphs were prepared with GraphPad Prism (version 5.03; GraphPad Software, San Diego, CA).

RESULTS

Of 227 patients recruited to the study, 224 were randomized and received their allocated treatment. Two patients inadvertently received unblinded antivenom rather than the trial drug and 1 did not have the trial drug code recorded. One hundred twelve patients were randomized to receive normal saline solution (placebo arm) and 112 to receive redback spider antivenom (Figure 1). The 2 study arms had similar baseline characteristics, although the placebo group tended to present earlier, had more patients with an initial pain score of 8 to 10, and had fewer patients who received previous analgesia (Table 1). There were 76 patients (34%) with systemic effects, and 176 patients (79%) developed diaphoresis (local [111; 50%], regional [31; 14%], and generalized [34; 15%]).

Two hours after treatment, 26 of 112 patients (23%) from the placebo arm had clinically improved pain versus 38 of 112 patients (34%) from the antivenom arm (difference in favor of antivenom 10.7%; 95% CI −1.1% to 22.6%; $P=.10$) (Table 2). The change in pain score for individual patients, comparing placebo with antivenom, is shown in Figure 2, and the percentage reduction in pain scores is shown in Figure 3 and Table 3. Additional analyses of the primary outcome using absolute (nonweighted) and relative measures of changes in pain had no significant difference between placebo and antivenom (Appendix E1, available online at http://www.annemergmed.com; Table 3). Systemic effects resolved after 2 hours in 9 of 41 patients (22%) in the placebo arm compared with 9 of 35 patients (26%) in the antivenom arm (difference 3.8%; 95% CI −15% to 23%; $P=.79$).

There was no significant difference between placebo and antivenom for the improvement in pain at 4 hours and 24 hours (Table 2). Figure 4 shows the change in pain during the study period, including pain on follow-up at 7 to 10 days and at 6 weeks. There was also no difference in the resolution of systemic effects between placebo and antivenom.

In total, 135 patients required rescue opioid analgesia, 77 receiving an oral opioid (oxycodone, codeine, or tramadol),

Table 1. Baseline characteristics.

Baseline Parameters	Placebo, n=112		Antivenom, n=112	
Age, median (IQR), y	40.0	(26.0–54.0)	39.0	(31.8–54.0)
Male	55	49%	59	53%
Baseline pain score*				
2–3	7	6%	10	9%
4–5	20	18%	22	20%
6–7	36	32%	42	38%
8–10	49	44%	37	33%
Spider identified	87	78%	84	75%
Bite site (n=109, 111)				
Distal limb	58	53%	70	63%
Proximal limb	26	24%	28	25%
Trunk/head/neck	25	23%	13	12%
Time to study treatment, median (IQR)	2.0	(1.1–9.5)	2.7	(1.0–14.8)
Time from analgesia to treatment, median (IQR)	0.5	(0.23–1.06)	0.5	(0.17–0.99)
Previous analgesia				
Yes	47	42%	58	52%
No	52	46%	49	44%
Not recorded	13	12%	5	4%
Diaphoresis				
Nil	24	21%	24	21%
Local	56	50%	55	49%
Regional	14	13%	17	15%
Generalized	18	16%	16	14%
Systemic effects	41	37%	35	31%

IQR, Interquartile range.
*One patient in the antivenom group had a baseline pain score of zero because there was a delay with the trial drug.

29 receiving parenteral opioids (morphine or fentanyl), and 29 receiving both. Fifty-nine patients received unblinded antivenom 2 or more hours after the study treatment. More patients in the placebo group received rescue opioid analgesia and unblinded antivenom, although these differences were not statistically significant (Table 2).

Combining the primary outcomes to measure those with either a significant reduction in pain or systemic features did not alter conclusions about the lack of effectiveness (30/112 [27%] in the placebo arm versus 41/112 [37%] in the antivenom arm; difference 9.8%; 95% CI −2.4% to 22%; *P*=.15). Using the registered primary pain outcome (with the statistical inconsistency) also did not change conclusions (21/112 [19%] in the placebo arm versus 31/112 [28%] in the antivenom arm; difference 9.8%; 95% CI −2.4% to 22%; *P*=.15). The median percentage pain reduction was 25% in placebo arm compared with 33% in antivenom arm (Figure 3; Mann Whitney *P*=.052). However, there was no relationship between percentage pain reduction and time from bite to antivenom in the antivenom arm (Figure E1, available online at http://www.annemergmed.com). Response rates were equally poor when confirmed (spider identified) and unconfirmed bites were compared (Table 3; Appendix E1, available online at http://www.annemergmed.com).

Acute skin-only (mild) hypersensitivity reactions occurred in 4 of the 112 patients (3.6%) who received antivenom and none in the placebo group. Twenty-one patients (9%) developed symptoms consistent with serum sickness and 5 of these presented to the ED or local physician. There was no difference in reports of serum sickness between patients randomized to antivenom and placebo, although slightly fewer cases occurred once the use of unblinded antivenom was accounted for (Table 2). Eighteen (8%) patients re-presented to either the ED (11) or their local physician (7), 12 of these for ongoing pain for symptoms of the bite. This did not differ between placebo and antivenom arms.

LIMITATIONS

A potential limitation of the study was the sample size being too small to completely exclude a small benefit. It is possible that a larger study might find a beneficial treatment effect of antivenom, but the effect is very likely to be small. This study was powered to detect a difference of 20% (Numbers needed to

Table 2. The primary and secondary outcomes for the study.

Outcomes	Number*	Placebo	%	Antivenom	%	Difference	95% CI
Primary outcome (pain 2 h)		26	23	38	34	10.7	−1.1 to 22.6
Primary outcome (systemic 2 h)	(n=41, 35)	9	22	9	26	3.8	−15 to 23
4-h pain reduction	(n=105, 106)	46	44	56	53	9.0	−4.5 to 23
24-h pain reduction	(n=105, 107)	57	54	67	63	8.3	−5 to 22
4-h systemic resolved	(n=41, 34)	23	56	21	62	5.7	−17 to 28
Rescue opiate		73	65	62	55	−9.8	−3 to 23
Unblinded antivenom		36	32	23	21	−11.6	−23 to 0
PRN analgesia		25	22	29	26	3.6	−8 to 15
Serum sickness		9	8	12	11	2.7	−5 to 10
Serum sickness (no unblind AV)†	(n=76, 89)	5	7	9	10	3.5	—‡
Acute reactions		0	0	4	3.6	3.6	—‡
Repeated presentations		11	10	7	6	−3.6	−11 to 3

AV, antivenom; *PRN*, pro re nata "when necessary".
*One hundred twelve unless otherwise stated.
†Serum sickness occurring in patients who did not also receive additional labeled antivenom.
‡Unable to calculate 95% CI of the difference between proportions because it requires at least six subjects in each cell.

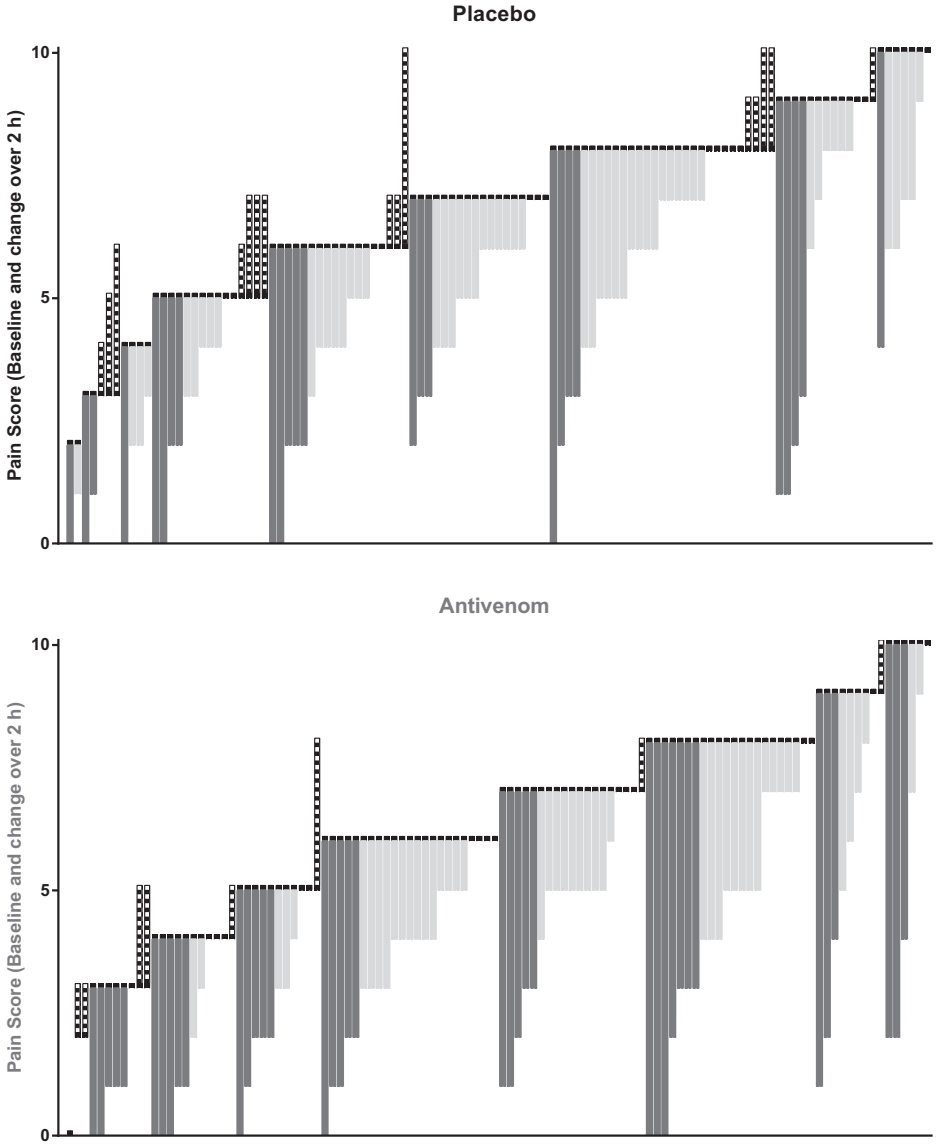

Figure 2. A waterfall plot showing all individual changes in pain score between baseline and 2 hours in each group, ordered according to baseline score and then response. Baseline score is shown as small black bar, and the vertical bars indicate the movement with worsening pain, shown as a checkered pattern and improvements shown in grey, with the darker grey indicating they met criteria for a significant change in pain scores (prespecified primary outcome).

treat [NNT] ≤5). It is important to consider that redback spider antivenom is used as an analgesic and not to save lives. The NNT in trials of effective analgesics ranges from 2 to 4 in meta-analyses.[16] Much higher NNT are not clinically significant for studies of analgesia. In other words, if the study were larger and showed a statistically significant and similar absolute difference in the order of 10% (NNT=10), 10 patients would need to receive antivenom for 1 patient to obtain significant pain relief. This is a very poor result for pain relief and also must be balanced against the risk of a hypersensitivity reaction of approximately 4% in this and previous studies (ie, numbers needed to harm=25).[2,17] Neither our standard analgesia nor analgesia and antivenom resulted in pain resolution in three quarters of the patients, so further trials are needed to investigate alternate and more effective treatments, whether or not antivenom has a marginal effect.

Another limitation of the study was that some cases were included according to a clinical diagnosis of latrodectism rather than a definite bite. However, our clinical definition has been validated by a prospective study of identified spider bites,[18] and reanalysis of the primary outcomes including only cases in which the spider was identified resulted in the same outcomes.

Finally, the outcomes we used have not been fully validated, which may have resulted in either underestimation or overestimation of the measured effect for both pain and systemic effects. However, this would have affected both arms of the study. A similar primary pain outcome has been used in 2 previous studies, one positive and one negative.[2,19]

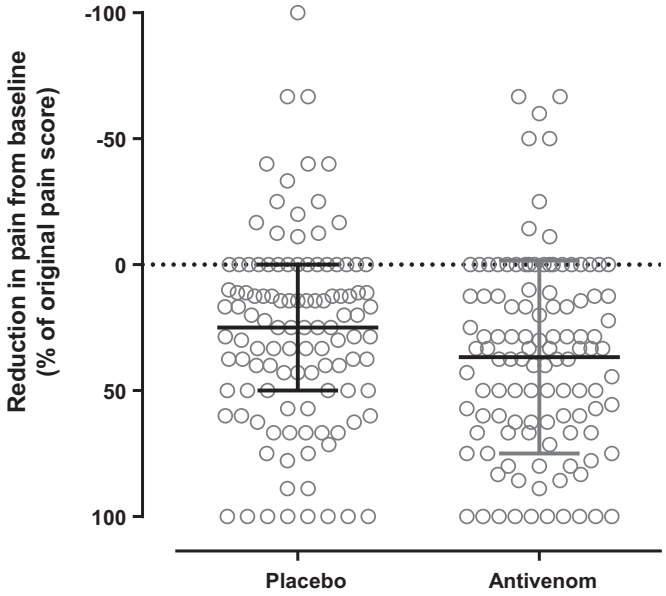

Figure 3. Scatterplot of the percentage change in the pain score from baseline to the 2-hour pain score comparing placebo versus antivenom, including lines marking the median and interquartile range.

DISCUSSION

This trial demonstrates that the addition of redback spider antivenom to a standardized analgesic treatment protocol in patients with latrodectism (redback spider envenoming) did not significantly improve pain or systemic effects. Patients responded poorly to analgesia alone or analgesia plus antivenom, with only a quarter of patients on average having an improvement at 2 hours. There were also no differences in secondary outcomes between the placebo group and the antivenom group.

The use of antivenom in latrodectism has always been contentious because it is not a life-threatening envenoming syndrome. Therefore, clear benefits of antivenom over standard care are required to balance against the known but small risk of anaphylaxis to the antivenom. In our study, more patients had an improvement in pain in the antivenom group at 2 hours, but this did not reach statistical significance and there was no evident treatment effect on systemic envenoming. Furthermore, there was also a slight imbalance between the placebo and antivenom arms of the study, with the antivenom group presenting somewhat later and with fewer patients having high initial pain scores (Table 1). This imbalance may favor the pain response in the antivenom group because later-presenting patients are closer to spontaneous recovery at randomization. Later presentation of the antivenom group could alternatively favor the placebo group if antivenom has a time-dependent effect, but there was no relationship between the time to antivenom and the pain response in the antivenom group (Figure E1, available online at http://www.annemergmed.com). This indicates that redback spider antivenom is not more likely to be effective if administered earlier, which is not consistent with the expected effect of antivenom.

A number of in vitro studies have demonstrated that redback spider antivenom is able to neutralize the effects of the venom.[20-22] In addition, Graudins et al[21] showed that redback spider antivenom was able to prevent in vitro neurotoxicity in a chick isolated biventer cervicis nerve-muscle preparation and lethality in mice, from a range of widow spider venoms. Daly et al[22] also showed that redback spider antivenom prevented the lethal effects of *L hesperus* and *L mactans*. It is therefore highly unlikely that poor clinical effectiveness in our study is due to the antivenom having poor binding or neutralization properties. The likely reason for treatment failure is that in vitro antivenom efficacy does not always translate into clinical effectiveness. The antivenom has not been shown to distribute to the peripheral site of the envenoming syndrome. Nor has it been shown to bind to the toxin at its site of action and reverse pathophysiologic changes. To be clinically effective, an antivenom must be capable of doing both, and there are several previous examples of antivenom that cannot reverse pathophysiology and are therefore not capable of significantly improving clinical outcomes.[23]

A better understanding of the pathophysiology of latrodectism is required so that effective treatments can be developed. This study and previous work suggest that standard analgesic treatment is also unable to provide relief for patients. Other treatments such as calcium, magnesium, and muscle relaxants have never been tested in a controlled way in patients.

Table 3. Additional primary outcome analyses and sensitivity analyses of the primary outcome.

Primary Outcome (Pain at 2 Hours)	Placebo	%	Antivenom	%	Difference	95% CI
Final definition (as per study)	26	23	38	34	10.7	−1.1 to 22.6
Original registered definition	21	19	31	28	8.9	−2.1 to 20
Median absolute change VNRS, IQR	2	0 to 3	2	1 to 4	0	0 to 1
Median relative change VNRS, IQR, %	25	0 to 50	33	12 to 66	8.3	0 to 20
Bites with definite spider ID	N=87		N= 84			
Final definition (as per study)	22	25	29	35	9.2	−4.5 to 23
Median absolute change VNRS, IQR	2	1 to 3	2	1 to 4	0	0 to 1
Median relative change VNRS, IQR, %	25	11 to 57	38	13 to 63	12.5	0 to 20
Absolute change VNRS >2	39	35	51	46	10.7	−2.1 to 23.6
Baseline pain (4 or greater)	N=105		N=101			
Final definition (as per study)	23	22	33	33	10.8	−1.4 to 23

VNRS, Verbal Numerical Rating Scale.

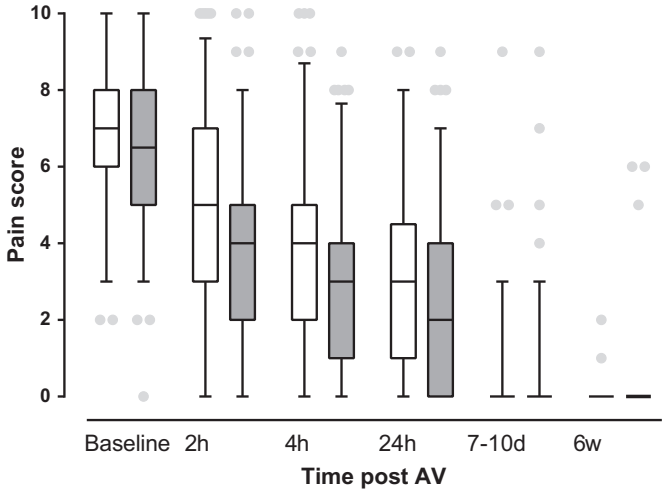

Figure 4. Box plots of the pain score for all points, including on follow-up at 7 to 10 days and at 6 weeks. Patients who received placebo are indicated in white; those who received antivenom, in grey. The boxes are the 25th to 75th percentile and the whiskers are 5th to 95th percentiles.

Potentially, treatments used for neuropathic pain, such as gabapentin, could also be tested.

The study cannot be immediately generalized to other widow spider antivenoms.[10] All widow spiders are closely related, and a recent study has shown that the redback spider (*L hasselti*) and both American black widow spiders (*L mactans* and *L hesperus*) contain similar neurotoxins to α-latrotoxin, originally identified in the European widow spider (*L tredecimguttatus*).[24] In addition, animal studies have demonstrated cross-neutralization of black widow spider venoms by redback spider antivenom.[21,22] The study therefore provides some support for the idea that widow spider antivenom may not be effective. The only other placebo-controlled randomized trial of widow spider antivenom also had negative results.[12] However, further and larger studies are required for different widow spiders and antivenom.

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APPENDIX E1.

Methods and Results

The definition of the primary outcome for pain severity involved a reduction in the VNRS that depended on the baseline starting point. Initially, this was defined according to a study conducted by Bird and Dickson[1] on the effect of the baseline visual analog scale (VAS) score on a clinically important detectable change in the VAS. We have previously defined primary outcomes based on the study by Bird and Dickson[1] that use the VAS, including both a positive- and a negative-result randomized controlled trial.[2,3] In this study, a VNRS was used to measure pain because in the previous RAVE-I study it was recognized that a VNRS was more feasible than a VAS in a study in multiple busy EDs. Previous research had demonstrated that there is good correlation between the 2 scores.[4] To allow for the categorical nature of the VNRS when using the baseline approach we had developed from Bird and Dickson,[1] the change in pain score needed to be a whole number (ie, 16 mm became 2 or greater, 33 mm became greater than 3, and 45 mm became 5 or greater). The registered primary outcome therefore had a clinically significant reduction in pain defined as 2 or greater for baseline scores of 0 to 3, greater than 3 for baseline scores of 4 to 6, and 5 or greater for baseline scores of 7 to 10. However, before unblinding of the study it was recognized that this would produce inconsistent results for some pain scores, eg, a person scoring 3 only needed a change of 2 (3 to 1), whereas a person scoring 4 needed a change of 4 (4 to 0). A slight modification was made so that a clinically significant reduction in pain was defined as 2 or greater for baseline scores of 0 to 3, 3 or greater for baseline scores of 4 or 5, 4 or greater for baseline scores of 6 or 7, and 5 or greater for baseline scores of 8 to 10.

In addition to the predefined definition of a clinically significant reduction in pain, the change in pain was also analyzed as an absolute change in the VNRS and a relative change (%) in the VNRS as sensitivity analysis. Further sensitivity analyses were conducted that included only cases in which the spider was definitely identified and also for patients with baseline VNRS of 4 or greater. The additional outcomes and sensitivity analyses are included in Table 3, and none were significant. The absolute difference in the median absolute change in the VNRS was 0, with 95% CI of 0 to 1 (Table 3), which does not cross 1.3/1.4 (equivalent to a minimally clinically significant difference defined as 13 mm or 1.4 cm),[1,4] so there is not a detectable minimally clinically significant difference between the 2 groups.

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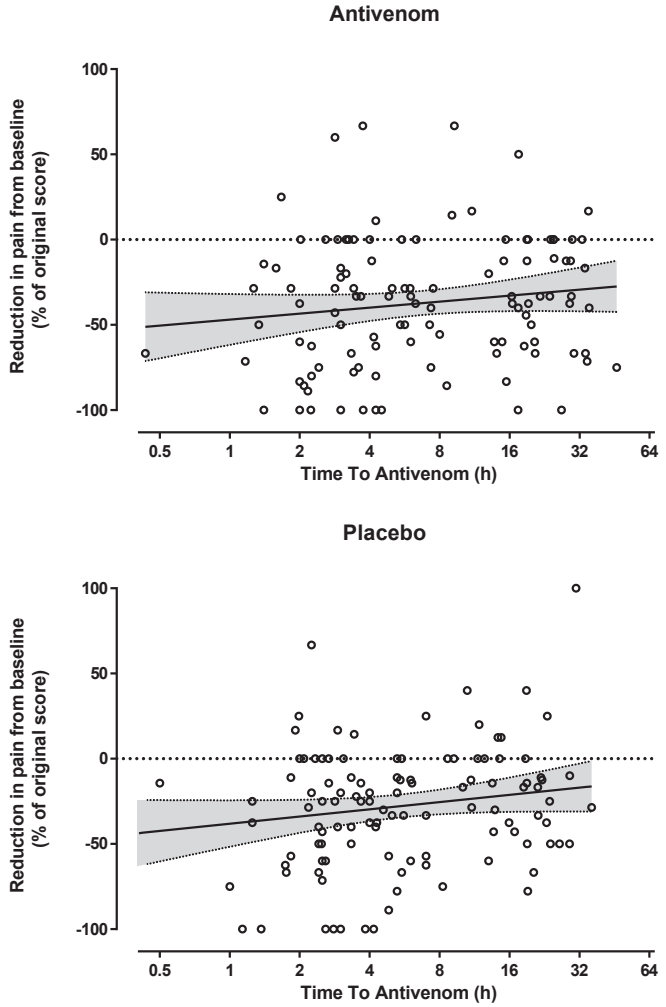

Figure E1. A linear logarithmic plot of the percentage reduction in pain for the antivenom arm versus the time from bite to antivenom (top panel) and the placebo arm versus the time from bite to antivenom (bottom panel). The solid line and shaded area represent the line of best fit by linear regression and the 95% confidence band.