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A randomised controlled trial of intramuscular vs. intravenous antivenom for latrodectism—the RAVE study

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Summary

Background: Widow spider-bite causes latrodectism and is associated with significant morbidity worldwide. Antivenom is given by both the intravenous (IV) and intramuscular (IM) routes and it is unclear which is more effective.
Aim: To compare the effectiveness of IV vs. IM redback spider antivenom.
Design: Randomized controlled trial.
Methods: Patients with latrodectism were given either IV or IM antivenom according to a randomized double-dummy, double-blind protocol. The first antivenom treatment was followed by another identical treatment after two hours if required. The primary outcome was a clinically significant reduction in pain two hours after the last treatment. A fully Bayesian analysis was used to estimate the probability of the desired treatment effect, predetermined as an absolute difference of 20%.
Results: We randomly allocated 126 patients to receive antivenom IV (64) and IM (62). After antivenom treatment pain improved in 40/64(62%) in the IV group vs. 33/62(53%) in the IM group (+9%; 95% Credible Interval [CrI]: –8% to +26%). The probability of a difference greater than zero (IV superior) was 85% but the probability of a difference >20% was only 10%. In 55 patients with systemic effects, these improved in 58% after IV antivenom vs. 65% after IM antivenom (−8%; 95% CrI: –32% to +17%). Twenty-four hours after antivenom pain had improved in 84% in the IV group vs. 71% in the IM group (+13%; 95% CrI: –2% to +27%). A meta-analysis including data from a previous trial found no difference in the primary outcome between IV and IM administration.
Discussion: The difference between IV and IM routes of administration of widow spider antivenom is, at best, small and does not justify routinely choosing one route over the other. Furthermore, antivenom may provide no benefit over placebo.

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Introduction

Latrodectism or widow spider-bite is arguably the most important spider bite syndrome worldwide. It occurs in most regions and although associated with a low mortality (<1%),[1–5] significant morbidity in the form of persistent pain and systemic effects can continue for days after the bite.[6] In Australia latrodectism is caused by the bite of the redback spider (*Latrodectus hasselti*) (Figure 1) and this is the commonest important envenoming syndrome in Australia. Antivenom is available in some countries including the United States, Australia, South and Central America.[7] Although the majority of antivenoms are administered intravenously (IV), the Australian redback spider (RBS) antivenom and some widow spider antivenom in Brazil are often administered by the intramuscular (IM) route.[7,8]

The most common reason given for using IM antivenom is that it is safer than IV antivenom, based on a study where there was a higher rate of immediate-type hypersensitivity reactions including anaphylaxis after giving antivenom as an undiluted IV bolus compared to IM administration.[5] This study is often quoted as supporting the view that IV RBS antivenom is associated with a higher incidence of reactions.[9] However, administration of undiluted IV antivenom is known to cause early complement-mediated reactions.[10] In our anecdotal experience, hypersensitivity reactions are uncommon when IV antivenom is administered slowly and diluted in normal saline.

In Australia there have been reports of RBS envenoming not responding to IM antivenom, prompting the subsequent use of additional IV doses with apparent success.[11] This is consistent with animal studies and clinical experience with other antivenoms.[12–14] There were no early controlled trials of RBS antivenom, and its use is based on anecdotal experience and a single retrospective study.[8] Wiener reported cases of RBS bites following requests to medical practitioners to supply information. He compared 109 patients receiving IM antivenom to 34 patients not receiving antivenom and found the duration of illness was shorter with antivenom.[8] This study is often quoted as demonstrating the effectiveness of IM antivenom,[15] but it was not based on definite bites and was a uncontrolled retrospective review of histories supplied by multiple doctors.

Figure 1. The Australian redback spider, *L. hasselti* (female) is the commonest medically important spider in Australia. It occurs commonly through out temperate parts of Australia, including a number of major capital cities where hundreds of bites may occur each year. Redback spider antivenom is the most commonly used antivenom in Australia.

The apparent effectiveness of IM antivenom may represent a placebo effect given that the subjective assessment of pain is used to measure treatment success. Following IM antivenom patients often report a reduction in pain within 10–30 min followed by increasing pain after 1–3 h.[11] This is not consistent with the expected pharmacokinetics after IM administration and can be further confused by the fact that the natural history of the bite is that the patient will get better.

A prospective observational study of RBS envenoming indicated that IM antivenom was no more effective than no treatment in a small group of patients.[16] Following this, a small RCT comparing IV and IM RBS antivenom reported no difference in pain scores at 1 h, but a greater proportion pain free in the IV group at 24 h.[17] The conclusions were limited by low study power and incomplete data. Unresolved questions about the effectiveness and safety required a larger RCT to compare IV and IM RBS antivenom. The aim of the study was to determine if the IV route of administration or the IM route of administration of RBS antivenom was more effective in treating the pain and systemic effects of redback spider bite.

Methods

We undertook a double-blind, double-dummy placebo-randomized controlled trial comparing IM and IV administration of RBS antivenom in patients with moderate to severe latrodectism (redback spider envenoming). The primary outcome was a clinically significant change in pain 2 h after the completion of treatment.

Study patients

Patients were recruited from the emergency departments of eleven Australian hospitals between 1 January 2003 and 31 March 2007. The study was

approved by human ethics research committees at all sites and was registered with the Australian Clinical Trial Registry, ACTRN012605000146695. All patients gave written and informed consent to the study.

Patients (8 years or older) were eligible for inclusion if the treating clinician had decided to treat with antivenom and the patient had a clinical syndrome consistent with latrodectism, including severe local pain (moderate envenoming) with or without systemic features (severe envenoming). Exclusion criteria were age <8 years, pregnancy, time since the bite was >24 h, previous hypersensitivity reactions to antivenom or inability to give informed consent.

Treatment protocol

When eligible patients were identified the study was explained to the patient and written consent obtained from the patient or patient's parent/guardian. They were put in an acute observation area on a cardiac monitor with non-invasive physiological monitoring (blood pressure and pulse oximetry) and an intravenous cannula was inserted.

Randomisation to either IV or IM antivenom was done in sequenced blocks of four (e.g. AABB) generated by a computer program. RBS antivenom vials were purchased from CSL Ltd. and PharmaLab Ltd. provided identical vials containing normal saline. Study packs were assembled containing two pairs of vials and each pair contained one antivenom vial and one normal saline (placebo) vial, labelled to be given either IM or IV according to the randomization list. Within each study pack both pairs of vials had the same allocation (antivenom to be given either IV or IM) so that each patient would receive one to two vials of antivenom by only one route. Study packs were distributed to all sites as blocks of four to be used sequentially. All the clinical investigators and treating doctors were blinded to the random allocation.

All patients received an IM injection of one vial and an IV infusion of the other vial made up in 200 ml of normal saline and given over 20 min. Repeated clinical assessments (see below) were performed at 30 min intervals after the completion of the IV infusion. After 2 h, a second study treatment was given if the treating doctor was not satisfied with clinical response to the first treatment. Repeated clinical assessments were performed at 30 min intervals from the completion of the second IV infusion for another 2 h. If the patient was still symptomatic 2 h after the completion of the second study treatment, they could be treated with further open-label antivenom at the discretion of the treating doctor. Patients were sent home with a sheet to record pain which they were asked to complete at 24 h. Patients were followed up by phone at 24 h and 7–10 days.

Data collection

Demographic data, details of the bite including whether a spider was identified by the patient and/or treating clinician and baseline observations were recorded (Table 1). To assess pain, a visual analogue score (VAS) was obtained by instructing the patient to make a vertical mark along a horizontal ungraduated 100 mm line at a position corresponding to the severity of their pain, the ends of the line representing 'No pain' and 'Worst pain possible', respectively. VAS, HR, BP, temperature, assessment

Table 1 Baseline characteristics of the two groups

	Intravenous group $N=64$			Intramuscular group $N=62$		
	Number	Percentage	95% CrI	Number	Percentage	95% CrI
Demographics						
Female	42	66	53–76	35	56	44–68
Age (years)[a]	40 (33–55)			38 (26–47)		
Spider Seen	47	73	61–82	44	71	59–81
Bite site: Limb	55	86	75–92	50	81	69–89
Clinical effects						
Baseline pain (VAS)[a]	62 (48–81)			64 (36–75)		
Radiating pain	55	86	75–92	49	79	67–87
Systemic effects	31	48	37–60	24	39	28–51
Diaphoresis[b]	41	64	52–75	45	73	60–82
Previous analgesia	27	42	31–54	24	39	28–51

95% CrI – 95% credible interval.
[a]Median and interquartile range; [b]local or regional diaphoresis.

of systemic symptoms and bite site observations were recorded every 30 min after the completion of antivenom. A subgroup of patients also had serial collection of serum for measurement of RBS antivenom concentrations (reported elsewhere[18]). Adverse events were recorded on a specific datasheet and symptoms/severity grading performed according to a previously published system.[19]

Data analysis

The primary outcome was a clinically significant reduction in severity of pain 2 h after completion of antivenom (one or two vials) based on the reduction in VAS. A clinically significant change was as defined by Bird and Dickson[20,21] and varied according to the baseline VAS. The data were analysed by intention to treat. Secondary outcomes were: a reduction in systemic effects, requirement for further doses of antivenom, clinically significant change in VAS (or verbal numerical rating score when the VAS was not obtained) at 24 h, administration of analgesia in hospital after commencing antivenom and use of analgesia after discharge. For analyses of secondary outcomes, cases were only included if they had data for the particular analysis—per protocol analysis.

The initial sample size of 40 in each arm was based on the expectation that there would be a large difference between IV and IM antivenom. The first interim analysis revealed a much smaller than expected difference so the sample size was increased to 200 patients in each arm ($P_0 = 0.5$, $P_1 = 0.65$, $\alpha = 0.05$, $\beta = 0.8$). Interim analyses were then planned at the end of each summer season and a Bayesian approach was adopted for deciding when to stop the study (Full details in the appendix).[22] We derived sceptical and enthusiastic prior probabilities for IV and IM antivenom being effective and combined one of these with the data depending on whether the study was showing a negative or positive outcome. These prior probabilities were derived from a survey of emergency physicians (see Appendix).[23] Early termination of the study was planned if there was a clear difference between the two treatments or there was a clearly negative finding based on the posterior probabilities derived from the data and prior probabilities.

Statistical methods

A fully Bayesian analysis of the data were employed to address the pre-existing polarization in views on the effectiveness of antivenom and to provide a more meaningful and clinically applicable interpretation of the results. The analysis was performed using WinBUGS 1.4 which is a Bayesian statistical modelling program that generates the posterior estimates and credible intervals (CrI) for the parameters of interest. The full details of the elicitation of the prior probabilities and the Bayesian analysis are included in the appendix. In addition a Bayesian meta-analysis was undertaken to combine the data from this study with the previous study by Ellis *et al*.[17]

Results

One hundred and thirty patients were recruited to the study, had an initial baseline assessment and were randomly allocated to IV or IM RBS antivenom. Three patients withdrew prior to the administration of antivenom because their pain resolved. A fourth patient was withdrawn after the administration of their first vial because their clinical history and spider description were consistent with a funnel-web spider bite (Figure 2). Of 126 patients available for the primary analysis, 64 patients received IV antivenom and 62 received IM antivenom (Figure 2). Systemic effects occurred in 55 patients (44%) of patients.

Primary outcome

The study was stopped at the beginning of the fifth year because of a negative finding clearly overcoming the enthusiastic prior probability. Two hours after completion of one or two vials of antivenom, 63% of the IV group had clinically improved pain vs. 53% treated with IM antivenom (+9%; 95% CrI: −8% to +26%). Using a non-informative prior probability, the probability that the difference between the proportions with clinically improved pain was >0% was 85%, but the probability that it was >20% was only 10%. The probabilities are demonstrated graphically in Figure 3 by their areas under the curve. When the data were combined with the enthusiastic prior probability the absolute difference only increased slightly to 10% (95% CrI: −6% to +26%) from 9% and the probabilities that it was >0% and 20% were 90% and 12%, respectively.

Secondary outcomes

The secondary outcomes are shown in Table 2. For the majority of the outcomes there was no significant difference between groups. However the IV group was less likely to receive additional doses of antivenom and more likely to have significantly improved pain at 24 h while the IM group was more likely to have improved systemic effects (−8%; 95% CrI: −32% to +17%). The adverse reaction rates were similar for the two routes of administration and there were no severe cases of anaphylaxis.

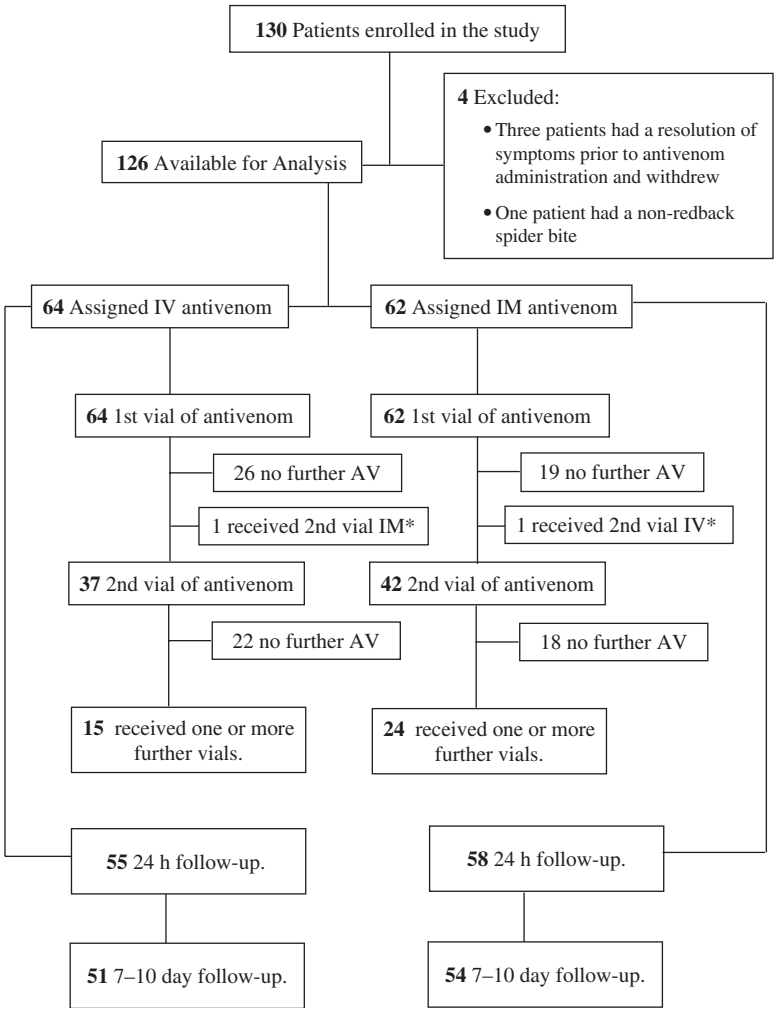

Figure 2. Flow chart of all persons recruited to the study including the dose received by patients in each arm of the trial and the number of patients followed up. AV, antivenom.

Meta-analysis

Data were obtained from the study by Ellis *et al.*[17] for the same primary outcome and used to derive prior probabilities. This was combined with the study data using a Bayesian meta-analysis and the posterior probability of success with IV antivenom was 55% compared to 51% for IM antivenom, with an absolute risk difference of 4% (95% CrI: −12% to +19%). The probability that the difference between the proportions with clinically improved pain was >0% was 68%, and >20% was 2%.

Limitations

The study was not large enough to exclude the possibility of a small difference between the IV and IM routes. However, the use of a Bayesian analysis allowed us to provide the probability for a number of different effect sizes based on clinically significant differences. In a survey of Australian emergency physicians on the treatment of redback spider envenoming, the emergency physicians reported that the median numbers needed to treat (NNT) they required to change from IM to the IV route was five, corresponding to an absolute difference of 20%. Our analysis shows that the probability of there being a 20% difference was very low (10%) providing good evidence that the difference between the IV and IM routes is not clinically useful. Further, a Bayesian meta-analysis that incorporated the results from this trial and the previous trial by Ellis *et al.*[17] showed that there was only a 68% probability that IV was more effective than IM and there was virtually no chance (2%) that the difference was >20%.

The study was stopped early. The approach taken was designed so that the study would only be continued until a negative or positive finding was sufficient to overcome clinical prior opinion. It could be argued that the study did not exclude

a clinically small but significant difference between treatments. However, our laboratory findings that RBS antivenom is not detectable in the systemic circulation following IM administration suggests that this study may be equivalent to a placebo controlled trial of IV antivenom, and that RBS antivenom by any route provides little benefit over placebo. The important implication for the treatment of latrodectism worldwide is that placebo controlled randomized trials of widow antivenoms are urgently needed.

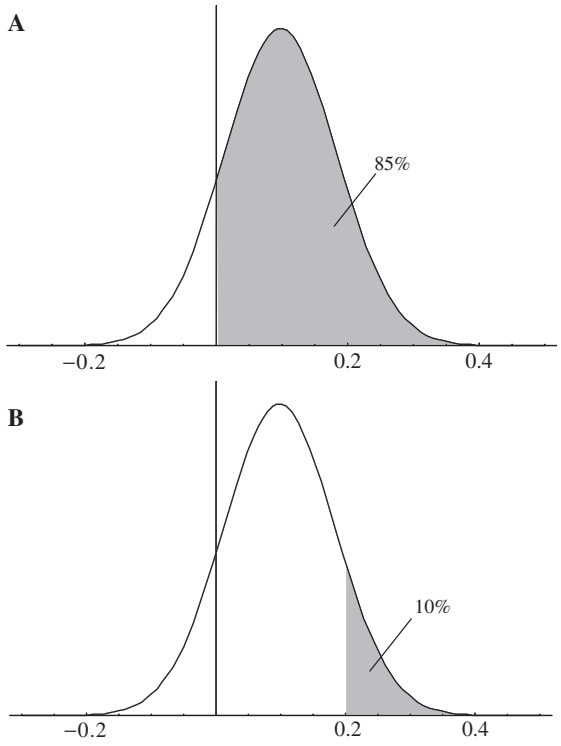

Figure 3. Probability distribution curve for the absolute difference between IV antivenom success and IM antivenom success with shaded areas under the curve representing the probability of the difference being >0 (**A**) or 20% (**B**).

Discussion

The study found the difference between IV and IM RBS antivenom in reducing pain 2 h after treatment to be small and less than the difference required by clinicians to favour the use of one route over the other. Some secondary outcomes also support IV being more effective, while others, such as the reduction in systemic effects, favoured IM administration. Combining the data from this study with data from a previous controlled trial[17] provided even less support that IV was more effective than IM antivenom.

Although one interpretation of the results is that IV and IM RBS antivenom are equally effective, the alternate and more concerning interpretation is that they may be equally ineffective. The latter interpretation is supported in several ways. A subgroup analysis of patients in this study in which serial blood samples were collected for the measurement of RBS antivenom concentrations has shown that antivenom is only detectable after IV administration.[18] In addition there has been at least a doubling of the dose of antivenom over the last three decades. The median dose in this study and the study by Ellis *et al.*[17] was two vials

Table 2 Outcomes for the study including the primary outcome, a priori secondary outcomes and adverse reaction rates in the two arms of the study

Outcome	IV group				IM group				Comparison	
	No.	Total	Estimate (%)	CrI	No.	Total	Estimate (%)	CrI	Absolute difference (%)	p[diff>0][b] (%)
Clinically improved pain at 2 h	40	64	62	50–73	33	62	53	41–65	9	85
Clinically improved pain at 24 h	50	59	84	74–92	41	57	71	59–82	13	95
Reduction in systemic effects	18	31	58	41–74	16	24	65	46–82	−8	27
Additional antivenom given	15	64	24	15–35	24	62	39	28–51	15	97
Analgesia given after discharge	24	55	44	31–57	29	58	50	38–63	−6	25
Opiate analgesia required after d/c	10	55	19	10–30	11	58	20	11–31	−1	46
Analgesia given in ED	22	61	37	25–49	20	61	33	22–45	3	65
Opiate analgesia required in ED	15	61	25	16–37	16	61	27	17–38	−2	42
Unable to sleep in first 24 h[a]	9	55	18	9–28	10	56	19	10–30	−1	42
Acute hypersensitivty reaction	2	64	5	0–11	2	62	5	0–11	−0.1	49
Serum sickness	5	51	11	4–21	8	54	16	8–27	−5	23

[a]Not defined as a secondary outcome a priori. [b]Probability that the difference (favouring IV) was greater than zero.

with 31% of patients receiving 3–6 vials in our study. This contrasts with the review by Sutherland *et al*.[5] in 1978 where the median dose was one vial and only 61 of 2062 (3%) received two or more vials. If RBS antivenom is effective, one has to question why the dose requirements are steadily increasing.

Despite RBS antivenom being given in a controlled fashion with regular assessment of pain and systemic features and further doses of antivenom given after measurement of the primary endpoint, 44–50% of patients took additional analgesia after discharge from hospital and about a sixth were unable to sleep in the first 24 h after the bite. These findings further question the effectiveness of the antivenom if using more than the recommended doses of antivenom still left about half of the patients requiring ongoing analgesia and a sixth unable to sleep. Finally, we would expect antivenom to have a greater treatment effect in patients with more severe envenoming, or in this case, patients with systemic envenoming. However, IM antivenom appeared to be more effective for systemic envenoming, opposite to IV antivenom being superior for the primary outcome.

The advantage of the Bayesian analysis is that rather than providing a point estimate of the absolute difference in the proportion of patients with a successful outcome we are able to determine a posterior probability that this difference is greater than zero, or more importantly, greater than a predefined NNT required by clinicians to justify a change in practice.

Interestingly, the estimates of treatment success for IV and IM antivenom by emergency physicians were all greater than either of the estimates from the data in the study. Therefore, despite disagreement about whether IV was better than IM, all prior estimates of the success of IV or IM were all greater than IV or IM in the study. When we combined the enthusiastic prior probabilities with the data, the posterior probability distribution changed very little compared to an uninformative prior probability of IV or IM success. This can be interpreted as the data being sufficient in the sense that it contributed more to the posterior probability and that the study data (likelihood of) truly overcame the enthusiastic prior probabilities.

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Appendix: Bayesian analysis

Elicitation of prior probabilities

Elicitation of prior probabilities required determining the beliefs and practices of clinicians. Discussion with emergency physicians and clinical toxicologists suggested a polarity in views about the administration route of RBS antivenom. Some believed that the IV route was more effective than the IM route ('enthusiasts') and others believed each route was equally as effective ('sceptics'). The Bayesian approach requires quantifying belief in the treatment effectiveness in a prior probability distribution, and combining it via Bayes' theorem with the likelihood from the study data to create a posterior probability distribution of the effect.

From published survey data[23] we produced histograms of the expected response to IVs and IM antivenom for both the sceptics and enthusiasts. Beta distributions were then fitted to each of these probability distributions by matching the mean and variance of the Beta prior probability distribution to the mean and variance of the enthusiastic and sceptical datasets. Beta distributions were chosen because they are conjugates to the binomial likelihood from the data.

Estimation of absolute effect difference

The proportion of patients who had clinically improved pain (primary outcome) in each group (IV and IM) were compared using a binomial model for treatment success with IV or with IM antivenom. The prior probability distributions and the IV and IM likelihoods of a treatment success (based on the data) were combined via Bayes theorem to give the posterior distributions for the probability of treatment success for the IV and the IM routes of administration (post-study probability). In the final analysis we used a non-informative prior probability and the enthusiastic prior probability developed from the survey of emergency physicians. We estimated the absolute risk difference as the mean of the posterior distribution for the difference between the probability of a treatment success with IV and with IM. From this latter posterior distribution, we then estimated the posterior probability that the risk difference was >0% and 20% corresponding to 'any difference' and a NNT of five, respectively.

The physician survey showed that the median NNT clinicians wanted to change from IM administration to IV administration was five so, primary analysis was the estimation of probability of a risk difference being >20%. This balanced the risk/costs of the treatment as defined by clinicians. All parameters of interest were estimated simultaneously in the statistical modelling process. All secondary outcomes were analysed in a similar way and the results presented as means and CrI of the estimated risk difference.

A Bayesian CrI is a range of values for the parameter of interest with which a given posterior probability can be associated and therefore a 95%CrI contains the true parameter value with probability 0.95. In contrast, an orthodox 95% confidence interval is constructed in such a way that, in a long run of repeated experiments and calculation of a confidence interval using the experimental data, 95% of the intervals will contain the true value of the parameter. When undertaking the analysis, it is useful to be able to establish the proposition that a given parameter is greater than the relevant value e.g. a log odds ratio in favour of a new treatment is greater than zero. This is calculating as the area under the posterior probability curve to the right of the

null value (Figure 3). Similarly, if a 95% CrI is completely to the right of the null value, the posterior probability is 0.95 or more.

The analysis was done using the Windows interface for BUGS (**B**ayesian inference **U**sing **G**ibbs **S**ampling)—WinBUGS 4.1. It is a Bayesian statistical modelling computer program which generates posterior estimates and CrIs for parameters of interest using Markov chain Monte Carlo (MCMC) numerical simulation methods. The full annotated code for the elicitation of the prior probability distributions and statistical modelling in WinBUGS is available from the authors.

Interim analysis and stopping rules

We also decided to use a Bayesian approach to decide when to stop RAVE by incorporating the enthusiastic and sceptical prior probabilities.[22,24] Each interim analysis was done in a similar way to the final analysis. The prior probabilities derived from the physician survey were combined with the likelihood of the data at each interim analysis. Both enthusiastic and sceptical priors were used. A positive study would have been stopped if the data were sufficient (large enough numbers and large enough effect size) to dominate the prior belief of the 'sceptics'—i.e. the study convinces the sceptics that the intravenous route is better than intramuscular route. A negative study would have been stopped if the data were sufficient to convince the enthusiasts that there is no clinically important difference between the two routes of administration.

Bayesian meta-analysis

For the Bayesian meta-analysis, the prior probability was derived from for the success of IV and IM antivenom in the study by Ellis *et al*. and was represented by a beta distribution. An intention to treat analysis was done using the same clinical outcome as RAVE at 2 h. Where results were missing at the 2 h time point the VAS at 1 h was used instead. Data were available for 30 of the 33 patients in the study by Ellis *et al*.[17], with 6 of 14 patients given IM antivenom having improved pain at 2 h compared to 4 of 16 patients given IV antivenom. The 'Elllis' prior probability was then combined with the likelihood of the RAVE data to produce the posterior probability which represented the combined results of the study by Ellis *et al*. and RAVE. This method of Bayesian meta-analysis has been described previously.[25]