In reply.

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In reply:

We are indebted to Drs. Mellick, McCollum, and Mellick for describing the use of paraspinal injections of bupivacaine for treatment of headache.[1,2] Indeed, it was their report that motivated us to perform this study. Their case series in adults and children showed promising and significant results, but the publication lacked a control group. Thus, we initiated our placebo-controlled study. The following is a response to each of their concerns.

First, we would have preferred to use bupivacaine for a more direct comparison with the reported case series, but our institutional review board requested that we use ropivacaine because of the increased risk of cardiotoxicity with bupivacaine. The references provided below refer to the relative potencies of ropivacaine and bupivacaine during epidural injection; these data have limited relevance to our usage. A systematic review of ropivacaine concludes, "Despite the lower potency (based on minimum local anesthetic concentrations) of ropivacaine than bupivacaine or levobupivacaine at lower doses, such as those used for epidural or intrathecal analgesia, ropivacaine has similar efficacy to these agents at higher doses such as those used for peripheral nerve block."[3] An editorial advocating ropivacaine use in children states, "In children, in order to achieve the same analgesic effect, a lower concentration of ropivacaine is required in comparison with the same amount of bupivacaine."[4] Also, there is less pain with intramuscular injection of ropivacaine compared with bupivacaine.[5] Regardless, these differences are not likely to have influenced the outcome of this study; our results were almost exactly the same for patients treated with placebo and ropivacaine. Even if ropivacaine is *relatively* less potent than bupivacaine, we would have expected at least some effect from treatment.

Second, the video clip reveals that the patient received prochlorperazine and diphenhydramine at home before presenting to the emergency department (ED) and thus could have improved from these medications, rather than the intramuscular injections; or the improvement could have been to the result of a placebo effect of the intramuscular injections; or the improvement could have been a result of the therapeutic mechanism favored by Dr. Mellick; or it may have simply been the right time for the patient to improve. It is impossible to know. This is the problem with anecdotal data.

Third, patients were enrolled only when their treating clinician considered intravenous medications specifically for treatment of headache; these patients typically had a chief complaint of headache, not headache as a component of "acute viral, respiratory, and febrile illnesses…." Indeed, fever was an exclusion criterion. Our article includes a lengthy discussion on the challenges of selection bias in a placebo-controlled trial. There is also selection bias within a case series: the original report described only 471 patients selected for injection among 2,805 ED patients with a discharge diagnosis of headache. Our article also discusses the potential for a difference in placebo response when a therapy is administered in the context of usual clinical care (when it is presumed by the patient and clinician to be beneficial) compared with administration in a placebo-controlled study, in which the patient knows there is a 50% chance of not receiving the active therapy and the very benefit of the "active therapy" is questioned by the equipoise presented during the informed consent process.

Fourth, Drs. Mellick, McCollum, and Mellick propose a specific mechanism involving a neuronal circuit that is, in part, mediated by neurons in the muscles of the neck. Why, then, did we find no difference in response to ropivacaine injection compared with normal saline solution? We favor a different mechanism, also mediated by neurons, synapses, neurotransmitters, and pathways

specific to pain that would respond equally to saline solution or ropivacaine injections, namely, a placebo mechanism.[6]

We were excited by the response rates documented in the authors' case series and were disappointed when we could not replicate them. However, our results make for a more interesting discussion of the power of placebo and the differences between case series and placebo-controlled experiments, including the biases inherent in both. We thank the authors for advancing the discussion.

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Fab Antivenom Controversy Continues

To the Editor:

A recent *Annals* article[1] reports effects of Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV) therapy on recovery of limb function in patients with copperhead snake envenomation, concluding that treatment with FabAV reduces limb disability 14 days after envenomation. However, we are concerned with the validity and clinical significance of the study findings and conclusions.

Data in Table 1 indicate that the 2 groups were not equal in regard to baseline demographic characteristics. Compared with the placebo group, the FabAV group had more adult patients (93.3% versus 82.8%), but fewer adolescent (6.7% versus 17.2%), black (4.4% versus 6.9%), and Hispanic or Latino patients (6.7% versus 13.8%). The groups also differed by method of snake identification. Such group differences indicate that randomization did not work well, perhaps because of the small sample size.[2]

The primary outcome of the study was limb function according to the Patient-Specific Functional Scale. However, a baseline Patient-Specific Functional Scale mean score was not reported at envenomation (Figure 2*A*). Unless scores in the FabAV and placebo groups were the same on presentation, it is uncertain that the difference at day 14 can be attributed to FabAV treatment. The baseline numeric pain rating scale was higher in the placebo group (Figure 2*E*), further indicating a disparity of baseline clinical characteristics after randomization. Therefore, the small observed effect on the primary outcome that was claimed as a result of FabAV treatment is possibly due to chance or selection bias.

Even if the results of this trial are valid, the 1.2-point increase in the Patient-Specific Functional Scale score suggests only marginal benefit. The reliability of the scale varies for different conditions and body areas.[3] In this