Reviewer’s report

Title: A Phase II Clinical Trial to assess the safety of Clonidine in Acute Organophosphate Poisoning

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Reviewer: Janet Wittes

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The major strength of this paper is the context of the study and the success of the authors in carrying it out. I deduce from the nature of the study that pesticide poisoning must be frequent in rural Sri Lanka. If so, then it is important to have easily available antidotes.

The paper has several weaknesses, which I hope the authors can rectify. My first question has to do with the control group. As I understand the study, 12 patients were randomized to placebo and 36 to clonidine. (See below for my questions about the randomization.) The authors do not explain why a placebo-controlled study was ethical here. Was the actual study atropine plus placebo vs. clonidine+atropine vs. placebo? The authors need to clarify this aspect of the design.

They also should, as referee #1 requests, describe more fully the prior evidence for clonidine.

Of interest would be a discussion of why so many cases of pesticide poisoning occur in Sri Lanka. One of the advantages of publishing in Trials is that the journal affords authors the opportunity to describe the context of the experiment. If the authors decide to resubmit, they should describe the background of the problem more fully, they should clarify the treatment in the control group, and they should give more justification of clonidine (see comments from Reviewer #1).

Both reviewers and I found the conclusions problematic. For example, the authors write:

Conclusions: Our findings suggest that clonidine is well tolerated at the two lowest dosing levels; higher doses are associated with a high incidence of hypotension requiring intervention. These initial findings support doing further studies to characterize the efficacy profile of clonidine as an alternative antidote in organophosphate poisoning.

The sample size is too small for such a conclusion. As referee #2 comments, even the word “suggest” is rather strong. My own interpretation is that the lack of adverse experiences in the lower two doses makes further experimentation at
those doses feasible, but given the problems at dose three and the fact that
doses two and three do not differ much from each other, any subsequent study
should proceed with caution.

As far as efficacy, the study is much too small to make any inference. P-values
here are not useful; confidence intervals more usefully describe the uncertainty.

I share the concern of referee 2 that the statistical analysis is “overkill” –
basically, I think the study shows that it is safe to move forward cautiously in
another trial with the two lower doses. The mortality and ventilation rates in the
placebo group are thankfully very low, so the authors should not make any
inference about efficacy and should be very cautious about conclusions
concerning safety.

The unblinded nature of the study is concerning to me. The baseline distribution
of pesticides is surprising. (The statistical tests the authors use here are not
correct; they should not do line-by-line tests but rather a test of the entire
distribution.). The data raise the question as to why the offending pesticide was
distributed as 7 in the placebo group and none in the high dose group for
chloryrifos and the opposite for dimethoate. This looks like a failure of
randomization. How exactly was the randomization performed? My guess is that
randomization was performed stagewise. The authors need to give a full
description of the process of randomization and provide some reasonable
conjecture about the very surprising distribution.

Table 4 shows the means and SDs of BP by dose and then the maximum and
minimum changes. Maxima and minima are notoriously poor summaries of data;
let us see more complete measures of variability of change.