Author's response to reviews

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

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Author's response to reviews: see over
Reviewer’s comments and responses:

Overall comment

The reviewers have focused a lot on the statistical interpretation, but it is clinical interpretation that is far more relevant to these data. The paper is reported to provide the first safety data on clonidine for this indication. Prior to this study there was no human data, now we have data from 36 patients. The drug didn’t cause any obvious life-threatening events but had to be discontinued frequently at the highest dose tested. Reporting this is the purpose of the study.

By convention, we have performed frequentist statistics but we have not based our conclusions on these, for this is not a hypothesis testing study. It would be irrational to focus the article around statistical tests of the “null hypothesis that there is no difference between the groups in the rate of adverse effects”, especially given the small numbers and the sequential enrolment to different dosing levels.

In terms of appropriate interpretation I think we are basically in agreement with all the reviewers that these data are a preliminary guide to likely appropriate doses. So we have generally revised the article to make this clearer.

Reviewer 1

Comment: A principal conclusion as stated by the authors is that "our findings suggest that clonidine is well tolerated at the two lowest dosing levels administered". However this statement appears too strong since it is unclear whether the trial is sufficiently powered to support it (even as a "suggestion"). That is, "absence of evidence" does not imply "evidence of absence". As the authors acknowledge, this particularly applies to the primary outcome measure, defined as the proportion of patients in each group who either ventilated or died. (It is well-known that the statistical power for comparing binary outcomes is generally much less than that for comparing continuous outcomes). The presentation of confidence limits about the major endpoints would have made this point clearer.

Response: While we agree with the quote from the Altman & Bland, it should also be remembered that a lack of statistical "evidence of absence" also does not imply "absence of evidence". Data on 36 patients provides more evidence than no data at all. Providing good evidence on the use of a drug for an indication involves a sequence of studies—typically as many as 8 to 12 studies. This is merely the first.

95% Confidence intervals were provided in the clinical outcome table (Table 3).

We have also changed the concluding statement in the abstract to "Our findings suggest moderate doses of clonidine in acute organophosphate poisoning can be used without causing frequent clinical problems but that higher doses are associated with a high incidence of hypotension requiring intervention."
Comment: In general, it is not surprising that there was no statistical difference in the primary outcomes based on intent-to-treat. Consequently a more accurate summary statement for the paper would be that the present study "presents no evidence against the conclusion that clonidine is not well tolerated at the two lowest dosing levels administered", i.e. that the results are largely inconclusive. Similarly it is unsurprising that baseline comparisons shown in Table 1 are all non-significant.

Response: We have rewritten the conclusion but avoided using a doubly qualified double negative in the interests of clarity.

Comment: Given the exploratory nature of the trial and the acknowledgement by the authors that is underpowered, the proposed statistical analyses, involving nonparametric tests (adding further to the problem of low power), repeated measures ANOVA and Bonferroni post-hoc corrections, seems to be "overkill".

Response: The statistical tests could all be removed, but they are conservative and illustrate quite well the flaws in the trial. So it is hard to see what would be gained. That is they indicate the baseline imbalance, they indicate the lack of certainty about the difference between groups in clinical outcomes, and the only 'positive' conclusion is that they illustrate the greater rates and extent of hypotension at the higher dose in two different ways.

Comment: I certainly agree with the authors that "further studies must be done to characterize `the efficacy profile of this product." However from a statistical perspective I am also not convinced that questions regarding the safety profile of clonidine have been adequately addressed by this small unblinded trial.

Response: We agree from both a statistical and a clinical perspective that all questions regarding the safety of clonidine for this indication have not been addressed. We don’t think we implied otherwise. Definitive data on safety will require Phase III trials, and this is a phase Ila study.

We think that this is also being taken completely out of context with respect to clonidine safety. This study is not the first examination of safety of clonidine (a drug that has been used for 50 years), it is the first use in this indication. We did not see anything different or surprising when it was used for this indication.

Other comments:

Comment: I believe "Dunn's test" should read "Dunnett's test"

While there is a Dunnett’s test, we used Dunn’s test which is a post Hoc test for Kruskal wallis (Prism v5.0).

Response: The use of multiple significance tests computed at many different time points in each of the three graphs comprising Figure 1 is wrought with problems of multiplicity and not good statistical practice. Performing fewer significance tests that focus on summary measures calculated for each patient would be much more informative.
We disagree. It is not a problem to use multiple statistical tests, it is a problem if they are incorrectly interpreted as if multiple tests were not performed. We chose this approach with a bonferroni adjustment because the overall summary statistics we felt would be very misleading. That is repeated measures ANOVA will assume that differences in parameters between the groups remain constant over the repeated measures. However the clonidine infusions were stopped when the blood pressure dropped, people were given fluid (and a few people died). Thus the ‘post-hoc test’ on the differences in the early drop in blood pressure seems an appropriate way to deal with this.

Reviewer 2

Comment: The main weakness of the study is that they did not make a strong case for doing the study. It is not clear to me that there is evidence demonstrating the benefit of clonidine in animals who were optimally treated with atropine and pralidoxime or at minimum in animals optimally treated with atropine.

Major Compulsory revision:

The authors must demonstrate whether the use of clonidine in patients is justified by research in animals that is in the same setting as the setting in patients.

Response: The high mortality associated with Organophosphate poisoning, despite current treatment with pralidoxime and atropine means further research into antidotes is required. In Sri Lanka, OP poisoning is the 5th most common cause of mortality and morbidity. It is also a large problem in many other developing countries in rural Asia.

The initial animal work done by Buccafusco et al 1987 shows the additive effect of clonidine with atropine in improving outcome. It also prevented late complications associated with OP toxicity. There is a biological rationale in that it reduces acetylcholine release. These points have been expanded in the revised introduction.

Comment: In the second paragraph of the discussion they state that there were no serious adverse events. That is not the case as all deaths and events leading to prolongation of hospitalization are serious adverse events (SAEs). Total SAEs per group must be added to Table 3.

Response: Most of the deaths occurred in patients who had ingested dimethoate, who then required immediate ICU care and later on ventilator support. Dimethoate has a high case-fatality compared to other OPs (Eddleston et al 2005); it is approximately 50% if the level of consciousness (GCS) is reduced at presentation (Davies et al 2008). Thus it is not at all surprising that some people died within the study. The deaths were not attributed to clonidine by the treating doctors. Further, none of the deaths occurred while clonidine treatment was in progress.

Conclusions need to be revised.

In my opinion the results of this trial are not sufficiently promising to justify a larger trial.

Our conclusion has been modified. These data are not to “justify a larger trial” but to indicate that clonidine administered in OP poisoning has an acceptable safety profile (i.e. if such a trial could be
done without causing obvious frequent adverse clinical effects) and that a further studies are needed to established definitely the efficacy and safety of clonidine in OP poisoning

Minor Essential Revisions.

There are a number of typographical errors that need to be corrected. eg. "For example, we found that blood pressure was measured twice more frequency in the active arm." For example, blood pressure was measured twice as frequently in the active arms as compared to the placebo arm.

Corrected

Quality of written English: Needs some language corrections before being published

Corrected

Editors comments:

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.

Yes. This information was in the submitted paper “Other than study medication, all patients received standard medical care under the hospital’s admitting consultant physician. This usually included titrated doses of atropine and pralidoxime chloride 1 gram 6th hourly for 48 hours”

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

Added in the introduction

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).

We have added some context for your readers who may not be aware of what is going on in the developing world with respect to pesticide poisoning. However, there have been many papers on this and thus we didn’t want to bore people with background. The simple facts are pesticide poisoning kills more people in Sri Lanka than all infectious diseases combined and remains the first five leading cause of mortality and Morbidity. However, Sri Lanka is not unique in this respect; Southern India, China and much of South-East Asia have major public health problems as well. It is estimated there are over 300,000 deaths every year.

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.

We have not made any inference about efficacy. We have revised the conclusions. The study is not to be interpreted in isolation but on the background of clonidine already being shown to be safe for use in other indications and with favorable animal data on efficacy.

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 chlorpyrifos 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.

Randomisation was by a computer program. Treatment allocation was effectively concealed. However as we have explained in the methods it was done in 3 sequential stages in a 3:1 ratio of clonidine to placebo. Thus there was not random allocation between different doses. That would not be possible in a sequential increasing dose study examining safety. This is the routine design of phase I studies that primarily aim to establish a safe dose. This study is essentially a phase I/II study or phase IIA study in drug-development terminology. We have discussed this in the revised limitations paragraph. (It is another good reason to be very circumspect about any conclusions about efficacy).

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.

The maximum change shown in the table is there to inform clinicians not statisticians - it is a measure of the severity of the most severe adverse effects noted in each group. The figures show means and SD over time and are about as complete a measure of the data as could be provided without providing every single patients profile. It is unclear what else could be provided to meet this request.