Author's response to reviews

Title: Fenoldopam use in a burn intensive care unit: a retrospective study

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Author's response to reviews: see over
Enclosed please find the revision to the manuscript entitled “Fenoldopam use in a burn intensive care unit: a retrospective study” for submission to *BMC Anesthesiology*. I would like to thank the reviewers for their insightful comments addressed below.

Dr. Colpaert –

- Major Compulsory revisions

Table 1: overall mortality 29%, whereas in the article it is stated to be 38% (29/77). I have corrected the mortality error, I apologize for the oversight.

The criteria used for starting fenoldopam is not mentioned. As fenoldopam is also used for hypertensive crisis, it is quite surprising that 25% of patients were on vasopressor therapy. It should be more clearly stated that the dose they used is the dose which is deemed to increase RBF without systemic effects (since not every country has approved the use of fenoldopam, which means some physicians are not familiar with the drug). I have added to the introduction and methods to address the criteria for starting fenoldopam. In general, initiation and discontinuing was at the discretion of the attending physician. Indications for fenoldopam in our unit are typically low urine output despite adequate resuscitation and rising serum creatinine.

Was there a maximum treshold of vasopressor need for starting fenoldopam. How was the increment in fenoldopam infusion guided in those patients with vasopressor use? Furthermore, it is not clearly stated at which time after burn trauma the fenoldopam was started. As patients tend to improve hemodynamically 48 hours after burn trauma (after the burn shock), it seems rather normal to expect them to become less vasopressor dependent. I have clarified how we administer the infusion in the methods section. We typically start low (0.03) and titrate up to 0.09 if the patient tolerates the infusion. I have also added in the results section that only 5/77 patients were started on fenoldopam within 24 hours of admission and 24/77 within 48 hours.

- Minor revisions
Too many tables, and too many figures. Some figures should be replaced by tables. This could be improved. I have deleted three of figures as they were indeed superfluous. I have also altered some of the tables to either add or subtract some not needed information. Thank you.

Figure 7: hours after initiation of Fenoldopam instead of Fn. I have change figure 7 (now figure 4) to read “fenoldopam”

- Discretionary Revisions

Table 4: IVF: is this an average of the 12 hours pre and post fenoldopam, as in fig 5 (probably not as these are not the same figures). The table was median and the figure was mean. I have deleted the figure.

Which resuscitation protocol is being used, this is not mentioned. Is there a protocol for adjustment according to urinary output? During the time of this study, we used the modified Brooke resuscitation protocol (2cc/kg/TBSA) for initial resuscitation.

Dr. Palmieri

- Major Compulsory Revisions

Although the authors state that all patients had AKI, a clear definition of what constituted AKI is not given. Please provide a clear and concise definition of the inclusion criteria, specifically in regard to how kidney function was defined. I have clarified our definition of AKI in the methods section. We used the AKIN criteria with the lowest serum creatinine during admission as the baseline.

Please clearly state the criteria for initiation and discontinuing of fenoldopam. I have added to the introduction and methods to address the criteria for starting fenoldopam. In general, initiation and discontinuing was at the discretion of the attending physician. Indications for fenoldopam in our unit are typically low urine output despite adequate resuscitation and rising serum creatinine.

Patients on hemodialysis or renal replacement therapy were excluded. Why? Were patients who progressed to renal replacement therapy (i.e. treatment failures) also excluded? I have clarified why we excluded those patients who received RRT in the limitations section of the discussion. In short, we believe RRT (we use CRRT in our institution) would have so muddled the results with its attendant changes in patient physiology and laboratory results that it would have been a difficult task to make anything sensible from the numbers. Did the patients fail prior to initiation of RRT (fenoldopam used as an adjunct to RRT) or did they progress to RRT inspite of fenoldopam? This is an excellent question. We plan to look into our concomitant use of RRT and fenoldopam to determine what the typical course is. Of note, most patients who are on RRT are also receiving fenoldopam at our institution.

What was the etiology of renal dysfunction? Was there a difference in
outcomes in sepsis vs. drug-induced problems? I have added to table 1 that 60% of this cohort of patients had a concurrent diagnosis of sepsis. There is much discussion in the literature regarding changing treatment algorithms based on the etiology of the renal impairment. In our patients there is likely a multifactorial etiology in most cases (sepsis, nephrotoxic drugs, and relative ischemia).

Although fenoldopam was used at times of instability in these patients, other therapies, such as antibiotics, surgical drainage, line change, ventilator changes, etc. also likely happened. What other changes in care occurred during the 48 hour period? Was the improvement due to fenoldopam or definitive treatment of the underlying problem? Fenoldopam was instituted when multiple other procedures and therapies were ongoing. All septic patients have their lines changed, antibiotics are started, fluids are increased or decreased, pressors are started, vent settings and modes are changed, and immeasurable other changes occur as part of their care. To prove a cause/effect relationship with fenoldopam will take a randomized controlled trial. This is clarified in our limitations section.

This would be a more effective study if a matched cohort with similar burn size, AKIN criteria who were treated without fenoldopam were compared to the group treated with fenoldopam. Admittedly a comparative cohort would be ideal. We tried to create one, but had problems finding matched controls during the study time period and we felt it unfair to compare the results to earlier patients given the frequent advances in burn care.

Why was a one-way ANOVA used? A one way ANOVA with repeated measures was used to adjust for the co-variants of repeating the same measures on the same subjects.

How does the cohort mortality compare to the predicted mortality for this size of burn injury? This cohort of patients with a median age of 37 (IQR 24-57), % TBSA of 40 (IQR 23-58), with 28% having inhalation injury (n=77) had a mortality of 38%. It is obvious that this mortality rate is higher than what would otherwise be predicted based on modern prediction models. We expected this due to the fact that we’ve selected out those with AKI. Thus, it is difficult to comment on how this cohort compares. In the Coca study (21) their mortality in a cohort of patients (n=88) with AKI was 26%. However, their average burn size was slightly smaller (36%TBSA) and largely did not have concomitant traumatic injuries (our population had a median ISS of 25). We believe only a randomized prospective clinical trial would be able to provide a valid group for comparison.

Similar arguments have been made for dopamine in the past. What is different about fenoldopam? Increased urine output does not necessarily equate to better
outcomes. We believe the renal selectivity of fenoldopam is a great benefit over that of dopamine. We will have to wait to see if we are right until a RCT has been resulted.

Please provide objective data other than urine output that supports improved renal perfusion. Is fenoldopam renal protective, or just acting as a diuretic? Improvement of renal blood flow is the mechanism proposed based on previous studies (Kien et al – 51). Given the retrospective nature of this study, the best data we can provide is that UOP increased and SCr decreased. Regardless of mechanism, it appears the addition of fenoldopam was associated with improved renal function. It is possible that fenoldopam be just be acting like a naturetic with a diruesis that results, however, if this were the only action, one would not expect a decrease in Scr. The retrospective nature of the study prohibits identifying cause-effect relationship.

Please provide a comprehensive list of fenoldopam side effects, toxicities, potential drug interactions to inform readers of potential dangers of the drug other than hypotension. I have added a paragraph to the introduction regarding drug interactions and side effects.

Mean volume of maintenance fluids for these patients (Table 4) was >300 ml/hr prior to fenoldopam. Please provide rationale behind this intravenous fluid rate. What was the calculated insensible loss for these patients? The mean volume of fluid infused is not normally distributed and is likely skewed by 1) the small number of patients who received fenoldopam as part of their initial resuscitation and 2) a majority of these patients were exhibiting septic physiology before initiation of fenoldopam. Additionally, patients were receiving multiple other infusions other than crystalloid (i.e. abx, pressors, electrolyte replacement, boluses).

Were there changes in mean arterial blood pressure with fenoldopam use? Systolic pressure is not always the best representation of perfusion. I have included MAP data in the results section. The MAP increased at 24 hours and this increase was sustained at 48 hours.

In Figure 4, urine output averages almost 80 ml/hr pre-treatment and approximately 90 ml/hr post-treatment with fenodopam. In general, 30-50 ml/hr of urine output is considered to be adequate after burn injury. Were these patients overhydrated? The patients were possibly overhydrated, to know for sure we would need a prospective trial. An excellent point.

Minor Essential Revisions

Please provide mean values with standard error as well as median with IQR.
for all values in Table 1. All tables now include mean with standard error as well as median and IQR.

Please provide table of AKIN stage and mortality. I have included table 2 which stratifies the patients by AKIN stage and mortality by each stage.

For Table 2,3,4 please provide mean and standard error for all fields. All tables now include mean with standard error as well as median and IQR.

Please provide error bars for AKIN stage (Figure 1). AKIN stage is a dichotomous variable, therefore no error bars. I have deleted that figure as I think it makes more sense as a table. Thank you for the suggestion.

In Figure 6 and 7, please provide error bars for the modified inotrope score and Vasopressor Dependency Index. Also, provide clarification of exactly which time points were statistically significant changes. I have provided the error bars for figures 6 & 7 (now figures 3 & 4) and clarified at which time point the change becomes significant.

Discretionary revisions

There are no figure titles or figure legends. I have included the titles and legends as appropriate for the various tables and figures.

Dr. Rocco – Thank you for input. No changes requested.

Thank you in advance for your time and consideration. Should you have any questions regarding this manuscript, please do not hesitate to contact me at john.simmons@amedd.army.mil or at (210) 916-0439.

Sincerely,

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