Peer Review File

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Reviewer

Comment: In most toxicology journals, NAC is written acetylcysteine and not n-acetylcysteine. I defer to the journal's copyediting.
Reply: Thank you for this observation. We are happy to change it is required by the journal. We can cite numerus articles that refer to the medication as N-acetylcysteine
Changes in the Text: None

Comment: I'd like to see an analysis of the cost saving if the hospital pharmacies would have delivered the time-tested 300 mg/kg regimen. You might find more cost saving there so, even in patient for whom NAC therapy was appropriate.
Reply: We agree with the reviewer; such analysis would be of value. But this study only included real patient charges and not calculated or speculated cost structure. This will be of value for our next step project, and we thank the reviewer for this insight
Changes in the Text: None

Comment: Title: reflect the purpose of the study. Could it be shortened?
Reply: Yes
Changes in the Text: changes were made to the title

Comment: NAC comparatively to other antidotes is not costly. Perhaps in the US it is due to cost billed to insurances
Reply: Although the cost of oral or inhaled acetylcysteine is low even in the US, the cost of the IV form is still high. For our hospital, the price that we pay per one gram is $30.66, which is much more expensive that the price we pay for the oral form which is $0.02 per gr dose 1533 times higher. This cost is true worldwide. We agree with the reviewer that the charges in the US for patients is much more inflated than anywhere else in the world, but the medication is still highly expensive.
Changes in the Text: None

Comment: you need to describe what variables are going to be used to calculate the costs.
Reply: a clarification was added to the abstract
Changes in the Text: Cost analysis was completed by the hospital billing department and utilized true cost charges. Total cost of hospitalization was calculated and total medication charges were evaluated separately using the hospital's group purchasing organization (GPO) pricing.

Comment: the savings of 253 891$ (put USD) represent what proportions of the total costs? This would also be an interesting information to add. Are these costs the ones billed to patients or the real costs to the hospital?
Reply: This was changed in the text as recommended, the cost saving is for patient charges not hospital cost
Changes in the Text: A potential savings to patients and insurers of 253,891.85 United States Dollar (USD)

Comment: 29 doses out of 56 subjects and would be nice to know how many of those overlap with doses who should never have been started.
Reply: We agree with the reviewer; this part is confusing to the reader. So we replaced in the text with a clearer format. So, we added the number of inappropriate high doses rather that number of subjects who received it.
Changes in the Text: Of the 346 total doses of IV NAC administered throughout the study, of those doses n=47 (13.6%) exceeded manufacturer maximum suggested recommendations. The higher doses where all related to subjects with body weight higher than 100Kg.

Comment: are this ED visits in the USA? 2011 is a bit dated, can you find a newer statistic?
Reply: We also agree with the reviewer that these numbers are from 9 years ago, but we were not able to find more reliable recent data. This part is not vital for the manuscript and can be removed if the reviewer request it.
Changes in the Text: We clarified that those are ED numbers in the US

Comment: do you know why hospital pharmacy opted for the 400 mg/kg regimen? If so, would be good to insert here.
Reply: This was based on a study from the university of Washington that reported the one bag system of 400mg/kg safer and more effective to use than the traditional multi-bag system (usually 3) which is the 300mg/kg system. Reference and explanation added to the text (discussion section).
Changes in the Text: Our hospital system elected to us this one bag system of 400 mg/kg due to the reported benefits of better tolerance, effectiveness, less interruptions, and fewer compounding errors compared to the multi-bag system

Comment: do you at all use the 2004 Daly article in Annals of Emergency Medicine? If so, can reference here.
Reply: Thank you for the suggestion, reference added
Changes in the Text: Reference added

Comment: what to you refer to when you write the poison centre? Your local poison centre? All poison centre, AAPCC? Please be specific.
Reply: National center
Changes in the Text: clarified in the text

Comment: A good reference for this, if you PCC uses it is the ACMT guidance document on when to stop NAC.
Reply: Thank you for the recommendation, reference will be added
Changes in the Text: reference added

Comment: do you mean when providers do NOT follow…?
Reply: Yes, they don't follow. This is mainly providers who refer to our hospital from rural areas. And that what made us think of doing this study.
Changes in the Text: None

Comment: It doesn't seem a lot the number of patients with APAP toxicity in four years.
Reply: yes, we agree with the reviewer. But those are the numbers that were seen in our institution. Poisonings with other medications are more common in our area.
Changes in the Text: None

Comment: why are pregnant women and prisoner excluded?
Reply: IRB requested those to be excluded during the first submission. We followed their directions. It didn't make much sense to us either. Thank you for agreeing with our initial design.
Changes in the Text: None

Comment: this paragraph is potentially the single most important methodological issue with your study: is it possible that patients started before 4h on the RMN still deserved NAC?
Reply: We agree with the reviewer. This was added to the study limitations. Please read below.
Changes in the Text: One other important consideration is the fact that some of the subjects who started the NAC treatment before the 4 hours' level being obtained, could have potentially needed the treatment, and the treatment would not be considered inappropriate. Despite that we elected to count those in the group of inappropriate uses of NAC as it is not possible to know where they belong, because the treatment will cause unreliability of the subsequent acetaminophen levels. This could have inflated the potential savings, if any of them did indeed need the treatment.

Comment: You mention this in paragraph 142 to 149 but it is unclear which patient you excluded from inappropriate NAC. You cannot conclude much if a subsequent APAP concentration was not done in 16 of them but you can look at basic kinetics to predict the likelihood of being under the RMN line. This needs to be fleshed out more.

Reply: The reviewer is right to be confused with those number, we added a clarification to table-2 that will make it easier to follow
Changes in the Text: table-2

Comment: Moreover, if they had a deliberate acute ingestion, wouldn't they have been seen by psychiatry? Maybe some of those were appropriately admitted to psychiatry? Again, to automatically decide their entire hospitalization inappropriate is a stretch that needs to be fleshed out and explained a bit more. This might inflate your data on potential cost savings.
Reply: This is also a valid point brought up be the reviewer. But our hospital does not admit medically stable psychiatric patients. This patient population is cared for by an affiliated group in a separate building with separate cost structure.
Changes in the Text: Our hospital does not admit medically stable psychiatric patients, even if the intention of ingestion was self-harm, subjects' hospitalization cost was considered inappropriate in the analysis if the admission was not medically warranted.

Comment: Line 114: staged: should be staggered. Small typo to correct
Reply: Thank you, changed in text
Changes in the Text: Staggered
Comment: I suggest making a table with 2 columns hospitalization and medications costs for each ingestion scenario and say what was deemed inappropriate and not etc. In text, it is confusing.
Reply: Table 2 was modified to be easier to follow
Changes in the Text: Table-2

Comment: I would write concordant instead of compliant.
Reply: Done
Changes in the Text: concordant

Comment: you need to explain how you go to that amount.
Reply: We tried to explain this in table-3 rather than having it more confusing in the test
Changes in the Text: None

Comment: you need to explain your costs more. Where all lab charges included or just those subsequent to the decision that you deemed was inappropriate? Explain if your emergency room charges are one fee or increase by length of stay and if this is related to time of day. Readers not familiar with your billing system may not be able to generalize to their settings without a clear idea of what are your costs and why.
Reply: We are happy to add more clarification on what had been calculated, but we believe the paragraph has all the information the reviewer has asked for. "This cost included facility charges,

laboratory test charges, medication charges, physicians' charges, but did not include emergency room charges as those were unavoidable costs for all subjects."
Changes in the Text: None

Comment: instead of poor adaptation, I would write poor compliance or concordance depending what you choose in line 142
Reply: Done
Changes in the Text: poor concordance

Comment: here you should discuss the 33% increase in total dosing from 300 mg/kg to 400 mg/kg by the hospital pharmacies why and the evidence (if any) behind that decision.
Reply: This was added to the sections with reference
Changes in the Text: Our hospital system elected to us this one bag system of 400 mg/kg due to the reported benefits of better tolerance, effectiveness, less interruptions, and fewer compounding errors compared to the 300 mg/kg multi-bag system

Comment: 227 you mention as a limitation the reliance on data documented due to the retrospective nature of your study, but you don't mention anywhere before in the manuscript how many charts had complete or incomplete data. That's part of results to include because if you have a lot of missing data, well how did you account for that in your analysis?
Reply: this is very valid point, but as we had no missing data (our data is points didn't depend much on provider documentation). This will be added to result. Thank you for pointing this out.
Changes in the Text: No data elements were missing from the medical records.

Comment: Figure 1: Why were the 2 prisoners not included in the study? If this is a question of consent, need to explain
Reply: This was explained above. It was the request of our Orb not to include prisoners or pregnant women.
Changes in the Text: None

Comment: Table-3 I am not sure what you mean by Lost Cost Savings: Perhaps potential cost savings would be better?
Reply: agreed, and changed.
Changes in the Text: Potential cost savings