Peer Review File

Article Information: http://dx.doi.org/10.21037/tp-20-358

Reviewer A

Comment 1

Overall opinion:

1. The failure rates reported in this manuscript are surprising.
    a. Multiple studies using single dose IN dexmedetomidine ± IN midazolam show a much higher success rate for a variety of procedures especially transthoracic echocardiography which is much more invasive than MRI, BAER, nuclear med scans...
        i. IN dexmedetomidine:
            1. Li BL, Huang JX, Zhang N et al. Intranasal dexmedetomidine for sedation in children undergoing transthoracic echocardiography study—a prospective observational study. Pediatric Anesthesia 25 (2015) 891–896.
            2. Miller J, Xue B, Hossain M, et al. Comparison of dexmedetomidine and chloral hydrate sedation for transthoracic echocardiography in infants and toddlers: a randomized clinical trial. Pediatric Anesthesia 26 (2016) 266–272
            3. Miller JW, Divanovic AA, Hossain MM, et al. Dosing and efficacy of intranasal dexmedetomidine sedation for pediatric transthoracic echocardiography: a retrospective study Can J Anesth/J Can Anesth (2016) 63:834–841.
            4. Reynolds J, Rogers A, Medellin E, Guzman JA, Watcha MF. 352 A prospective, randomized, double-blind trial of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response (ABR) testing. Paediatr Anaesth. 2016;26(3):286-293.
            5. Olgun G, Ali MH. Use of Intranasal Dexmedetomidine as a Solo Sedative for MRI of Infants. HOSPITAL PEDIATRICS Volume 8, Issue 2, February 2018.

6. Baier NM, Mendez SS, Kimm D, et al. Intranasal dexmedetomidine: an effective sedative agent for electroencephalogram and auditory brain response testing. Pediatric Anesthesia 26 (2016) 280–285.

ii. IN dexmedetomidine + IN midazolam

1. Behrle N, Birisci E, Anderson J, Schroeder S, Dalabih A. Intranasal Dexmedetomidine as a Sedative for Pediatric Procedural Sedation. J Pediatr Pharmacol Ther. 2017;22(1):4-8.
2. Fett J, Hackbarth R, Boville BM, et al. Comparative Effectiveness of Intranasal Dexmedetomidine–Midazolam versus Oral Chloral Hydrate Targeting Moderate Sedation during Pediatric Transthoracic Echocardiograms. J Pediatr Intensive Care 2017;6:182–187.
3. Greenberg B, Schoonover J, Jedliki K et al. Intranasal Combination Dexmedetomidine and Midazolam for Pediatric Procedural Sedation. Society for Pediatric Anesthesia Conference 2010.
4. Using IN DEX + IN MID, unpublished data from our large sedation center show:
    a. MRI/AABR success rates for < 12 months of age: >90%
    b. MRI success rate for > 12 months of age: ~60%
    c. Nuclear med scan success rates < 6 months of age: 100%

Reply 1

Our study was conducted with the use of IN dexmedetomidine as the sole sedative. The overall result of our study was initially surprising to us. On further analysis, we found that the success rates of completion of AABR, CT, DMSA, MAG3 scans were comparable to previously published data with the use of IN dexmedetomidine alone. The failure of sedation in long procedures was contributed mainly by the low success rate of MRI scans. Contributing factors to these were postulated in the discussion. This includes various external factors unique to how MRI scans being conducted, such as placement of ear plugs, head caps and transferring of beds. Anecdotally, delays in the schedules of MRI scans were also more common. However, we did not collect data for these events.

Changes in text

We have further improved our discussion in view of the above. However, specific results about the latter events were not able to be provided.

Comment 2

2. Based on the listing of already published data listed above, this manuscript does not provide new data RE: overall success rate or dosing.

Reply 2

Our study compared success rates across different procedures in a real-world setting – something that was not well represented in previous papers. Dosing was not statistically significant as factor that influenced success rates in our paper. The authors believe that a key learning point from this study is that choice of procedures is important for successful use of IN dexmedetomidine.

Changes in text

We have elaborated on the key findings of our study in the discussion.

Comment 3

3. What this manuscript has the potential of providing is a description of patients/procedures that may do well with IN moderate sedation. The authors would really need to control for the following factors in order to get an accurate assessment of which patients have a higher likelihood of success with IN moderate sedation:
    a. Time to adequate sedation: as the authors note they may not have allowed adequate time for the patients to reach an adequate level of sedation. The authors should provide data RE: times in those who had a successful sedation and those who failed.
        i. Miller et al (retrospective study) suggest it took 20-30 minutes to reach adequate sedation to complete a transthoracic ECHO (TTE), though in the prospective study it only took 13-14 minutes.
        ii. Fett et al showed an average of almost 38 minutes to reach adequate sedation to complete a TTE.

iii. Baier et al reported 25 minutes to reach adequate sedation to complete AABR and EEG.

b. Age/weight: It is surprising that the authors found younger and smaller patients had higher failure rates. In our unpublished data the failure rate increases with age > 30 months and weight > 30 pounds. This finding of theirs would need further data to verify.

c. Other factors that our experience suggest contribute to increased success rates:
   i. Patients who come in to the sedation suite sleeping are much less likely to complete the studies with our moderate IN sedation regimen. We ask parents to keep their children awake for several hours before the sedation.
   ii. Patients getting MRIs due to a seizure disorder are more successful when they are allowed to take their meds even during the NPO period.
   iii. Patients who are kept NPO much longer than the required length of time are less likely to succeed. We encourage parents to feed their children right up to the NPO time.
   iv. Patients with profound sensorineural hearing loss don't do well with IN moderate sedation; we suspect they are more sensitive to any stimulation.

Reply 3a

In our discussion, we mentioned that we may not have allowed adequate time for the patients to reach an adequate level of sedation. Our observation is that even though patients reach a modified Ramsay score of 3, they may still not be adequately sedated for handling, such as movement to a new bed, replacement of monitoring devices such as blood pressure cuffs or pulse oximetry. Perhaps, a modified Ramsay score of 4 should be reached before such handling was to occur. As suggested, we have included the analysis of onset of action and total duration of sedation between the two groups in the revised manuscript.

Changes in text

We have analysed the onset of action and duration of sedation between the two groups and provided the details in the following:

- Page 12, lines 222 to 226
- Table 1

Reply 3b

We have re-analyzed our data for age and weight. Although these two variables were significantly different when compared as baseline characteristics, this was lost on multivariate analysis. The general trend from our study did show younger and smaller patients were at high chance of failure. This could be because sleep deprivation, which was routinely instructed for all our patients, was more difficult to comply in younger children due to parental perception.

Changes in text

We have modified our text as advised. Please see page 15, line 286 to 296.

Reply 3c

Thank you for sharing your experience. In our center, patients were phoned the day prior, and sleep deprivation was reinforced the night before their procedure and on the day of the procedure. Parents were also encouraged to discuss about the procedure with their children, so they are also mentally prepared. Nil by mouth timing was kept to a minimum. All medications were allowed with sips of water.

Comment 4

1. Abstract
    a. Line 49: 'borderline for statistical significance' should be 'did not reach statistical significance'.

Reply 4

Changes have been made in the text.

Changes in text

We have modified our text as advised: Page 5, lines 94 to 96

Comment 5

2. Background
    a. Line 72: dexmedetomidine is felt to have both central and peripheral nervous system effects, though it is true the sedative effects are centrally mediated.
    b. Line 83: many sedative agents including inhaled general anesthetics have animal model concerns for neurotoxicity, not just the listed agents.

c. Line 113: there is a little disconnect here. The manuscript says, 'Available sedatives included IV propofol, midazolam, ketamine and oral chloral hydrate.' Thereafter it states that dexmedetomidine was administered. How was the sedation drug chosen? Too much bias could be included at this point in the decision tree.

Reply 5

Changes based on this input have been made in the text.

This was a retrospective analysis of sedation cases. As per routine clinical practice, the choice of sedatives was left to the discretion of the physician. This is also recognized to be the limitation of this study. Factors which could influence this decision were included in the amended manuscript.

Changes in text

We have amended the text as advised: Page 7, line 131; Page 8, line 173 to 175.

Comment 6

3. Methods
    a. Line 110; '…as well as a paediatric intensive care' is a fragment that requires an object such as physician or provider.
    b. Line 124: need to better define 'waking up from sedation.' Does this mean opening eyes, able to eat/drink…?
    c. Statistics:
        i. line 154: should be StataCorp
        ii. lines 153-161:
            1. From Table 4, it appears that univariate logistic regression was also used, this should be mentioned in the methods.
            2. From Table 2 and lines 177-178, it appears that age, weight, and total duration of procedure are not normally distributed. For a better representation of the distribution, these should have been presented as the median, along with either the min/max, or the interquartile range.
            3. line 160: the "clinically relevant variables" should have been listed here.

Reply 6

Changes have been made in the text.

Changes in text

Page 8, line 170;

Page 9, line 189 to 190;

Page 11, line 229;

Page 11, line 233 to 237

Table 1 and 2

Comment 7

4. Results
    a. Numbers starting out a sentence should be spelled out.
    b. lines 165-175: there is no reason to list all the demographic details in the body of the manuscript since they are already in Table 1. Including all the CI and p values in the text is redundant and makes the reading laborious.
    c. line 172: NJ placement and ophthalmic examinations should not be included since they are not non-invasive procedures.
    d. line 173: As mentioned in Table 3, sedation success is 55.0%, not 55.1%.
    e. line 206: p value is listed here as 0.577, but in Table 4 is listed as 0.117.
    f. line 213: Odds ratio and 95% CI listed here are different from what are listed in table 4.
    g. line 215: no hemodynamic data is presented anywhere which makes this statement suspect since most papers do report changes in HR and BP with the use of dexmed.

Reply 7

We acknowledge your comments, and relevant changes have been made. NJ tube placement and ophthalmic examinations have been excluded in the revised manuscript and analysis. Though hemodynamic data was not collected for this study, the presence or absence of adverse events (including haemodynamic instability and desaturations) was analysed. We have added in the definition of adverse events in the revised manuscript.

Change in text

Page 12, line 246 to 257, line 261;

Page 10, line 192 to 197

Comment 8

5. Discussion
    a. line 236: definition of the abbreviation 'i.v.' should occur at the first mention of it (in the background)
    b. line 236; for consistency the abbreviation should be IV to match IN
    c. lines 279-284: there is no data presented suggesting that there was a delay between the MRI patients reaching a Ramsay score > 3 and the start of the scan. If this were to be shown then it could be argued that this were a failure in the system (unable to time things properly) rather than a failure of the sedating agent.
    d. lines 286-289: data should be provided to support this statement RE: dose and MRI. One would need to look at the percentage that succeeded vs failed with the lower dose.

Reply 8

We acknowledge the comments on abbreviations and edits have been made. With regard to delays on MRI scans, this was on the basis of anecdotal observations. No recordings of time delays due to technical or logistical challenges were made. The authors belief is that certain procedures (such as MRI scans) are more prone to technical delays systematically. This could reduce the efficacy of use of IN dexmedetomidine in these settings.

Comparison of dose of IN dexmedetomidine used in completion of MRI scans were made with prior studies, in which 4mcg/kg was associated with better outcomes and lower rate of anaesthetic rescue. The mean dose we have used for our study was 3.2±0.5 mcg/kg. When analysed by those who successfully completed MRI scans with those who did not, the results were not statistically significant ($p = 0.518$). Hence, we postulate that a higher dose is needed for a higher success rate in completion of MRI scans when using IN dexmedetomidine alone.

Changes in text

Page 7, line 142

Comment 9

6. Tables
    a. Unnecessary to repeat most of the non-statistically significant data in Table 2.

Reply 9

We acknowledge the comment and have deleted the original table 2.

Changes in text

Table 2 deleted.

Reviewer B

Comment 1

1) Methods

- Page 4, lines 111-112: Is it possible to mention the factors used in the choice of sedatives by the physician? How many physicians participated in this study? Describe better this topic.
- Page 5, lines 133-134: Why did you chose the cut off 60 minutes?
- Page 8, line 213: Please check these values: (95% CI 0.94-26.18; p=0.059). This is not the date presented in abstract and in table 4.

Reply 1

We acknowledge the comments on the physicians participating in the study and factors which could have influenced their decisions. Further detail about the nature of sedation in our center was also described in the revised manuscript.

A cut-off time of 60 minutes for categorizing procedures as long or short was decided based on institution protocol. It allowed the procedures to be dichotomized into two distinct categories. We have also amended all the discrepant values.

Changes in text

Page 8, line 171-175

Page 10, line 207

Page 13, line 288-293

Comment 2

2) Discussion

-Discussion is too long and lacks a critical reflection about data. Please rewrite it.

For example, the first two paragraphs only bring what the literature says about dexmedetomidine, without mentioning anything from the present study.

The third paragraph is adequade.

The fourfth paragraph brings data mentioned in the results section and cites table, and these are not appropriate.

Reply 2

We acknowledge the comments regarding the discussion and have improved the writing for clarity and conciseness.

*Changes in tex*t

Page 14, line 364 to 451