UAMS Journal Club Summary
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Dexmedetomidine as an Adjunct for Pediatric Procedural Sedation

Critical Bottom Line:
The two publications discussed below reached similar conclusions, advocating for the use of a combination of intranasal dexmedetomidine and ketamine. There does not appear to be a high rate of adverse events when using a combination of intranasal dexmedetomidine and ketamine; however, there does not appear to be significant improvement in sedation times or mortality risk when using a combination compared to using a single agent alone. These conclusions are difficult to draw due to the absence of a control group in Trial 1. Based on these trials, we can not recommend the use of a combination of intranasal dexmedetomidine and ketamine due to lack of evidence and lack of a randomized control trial comparing specific agents against one another.

PICO
P - Pediatric patients undergoing procedural sedation
I - Combination of intranasal dexmedetomidine and ketamine
C - Compared to single sedative agent
O - Rate of successful sedation and adverse events

Background:
Sedation for highly anxious pediatric patients is often required for diagnostic and therapeutic procedures. Ketamine has been used for procedural sedation, but it has some undesirable side effects (nausea, hypertension, and tachycardia). Dexmedetomidine is useful as a sedative and offers the advantage of having both sedative and anxiolytic effects, as well as relatively mild analgesic properties and a relatively short elimination half-life. Dexmedetomidine has been useful by the intranasal route, but has some drawbacks in terms of effectiveness, onset and offset time. A combination of dexmedetomidine and ketamine can effectively increase the speed of onset of sedation, thereby eliminating the slow onset time when dexmedetomidine is used as the sole agent. Combination of ketamine and dexmedetomidine by the intranasal route has not been widely reported, but is logical because the effects of the drugs are complementary.

Trial 1

Yang, F, Liu, Y, Yu, Q, et al. Analysis of 17 948 pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine. *Pediatr Anesth*. 2019; 29: 85– 91. https://doi.org/10.1111/pan.13526

Wiley Library Link: https://onlinelibrary-wiley-com.libproxy.uams.edu/doi/10.1111/pan.13526

The Basics:
This study was a retrospective observational case series completed in a large hospital in China between April 2016 and October 2017. This case series followed 17,948 pediatric patients who underwent procedural sedation using a combination of intranasal dexmedetomidine and ketamine. Most patients were undergoing MRI, EEG, doppler ultrasound, and other non-painful procedures. All patients were evaluated by an anesthesiologist and the combination of drugs was used unless there was a contraindication (see below under exclusion criteria). Consistent weight-based dosing was used with 2mcg/kg dexmedetomidine and 1mg/kg ketamine. Level of sedation was assessed after 30 minutes using Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score with a goal of less than or equal to 3.

Inclusion Criteria:
Patients undergoing procedural sedation from April 2016 - October 2017 who used a combination of dexmedetomidine and ketamine for procedural sedation - 17,948 patients (majority age <5).

Exclusion Criteria:
- Patients who did not receive combination of drugs
    - Allergies to dexmedetomidine or ketamine
    - Renal or hepatic dysfunction
    - Symptomatic airway obstructions
    - Severe cardiac arrhythmias such as II- and III-degree heart block
    - Intracranial hypertension
    - Anatomical anomaly of the nasal cavity
- Route of administration was not intranasally
- Dose was not 2mcg/kg (dexmedetomidine) or 1mg/kg (ketamine)
- Patients had incomplete data

Results:
In this large retrospective observational study with 17,948 patients, the rate of intranasal sedation success was 93% (16691/17948), intranasal sedation rescue was 1.8% (322/17948), and intranasal sedation failure was 5.2% (935/17948). Sedation success was defined as successful completion of the diagnostic examination and obtaining adequate diagnostic-quality images and reports. Intranasal sedation success, rescue, and failure were respectively defined as sedation success with a single intranasal dose, additional bolus dose, and the need for intravenous (IV) medications/inhalation agents. Median sedation time was 62 min, median time for onset of sedation was 15 min, and median sedation recovery time was 45 min. Incidence of adverse events was low (0.58%; 105/17948), with major and minor adverse events being reported in 0.02% (4/17948) and 0.56% (101/17948) patients, respectively. Postoperative nausea and vomiting was the most common (0.3%; 53/17948) minor adverse event. No deaths reported.

Limitations/Bias:

Unable to draw conclusion from this study due to this study being an observational case series and the absence of a control or comparison group. This study did have a great safety profile with few adverse events (documented very well) and no deaths despite very large sample size. Limitations include: different patient population (pediatric patients at a large hospital in China), controlled sedation setting (done under anesthesiologist with constant monitoring), procedures done not painful (not probably something that we would do in the Emergency Department). Overall, we would need more studies to be able to draw any conclusions.

Trial 2

Poonai N, Spohn J, Vandermeer B, et al. Intranasal Dexmedetomidine for Procedural Distress in Children: A Systematic Review. Pediatrics. 2020;145(1):e20191623 DOI: 10.1542/peds.2019-1623

Pubmed link: https://publications.aap.org/pediatrics/article/145/1/e20191623/36980/Intranasal-Dexmedetomidine-for-Procedural-Distress

The Basics:
This study was a systematic review encompassing 19 published and unpublished randomized trials, to determine the efficacy of intranasal dexmedetomidine (IND) for procedural distress in children. Primary outcome was the proportion of participants with adequate sedation. Trials included painful and nonpainful procedures, as well as different routes and doses for both IND and comparator drugs. IND was found to be more effective than other monotherapies included but inferior to oral ketamine and IND combined with ketamine. Higher doses of IND were also considered more effective compared to lower IND doses in four studies. Overall, IND appears to be an efficacious agent with the drawback of increased cardiovascular adverse effects, specifically bradycardia, when compared to other agents included in the studies.

Inclusion Criteria:
Published and unpublished randomized trials that involved intranasal Dexmedetomidine monotherapy versus a non-IND comparator. Trials for procedures, including children less than 19 years old were used. Trials that had both adults and children were also used, if the data had pediatric-specific stratifications.

Exclusion Criteria:
Substudies, crossover studies, abstracts with insufficient information and studies of anesthetic premedication unless they involved a painful procedure.

Results:
IND was deemed superior to oral chloral hydrate in three trials, oral midazolam in one trial and intranasal midazolam in one trial. Adequate sedation was reported in 33 of 41 participants (80.4%) for IND plus oral ketamine, 1086 of 1362 (79.7%) for IND, 241 of 318 (75.7%) for

chloral hydrate, 28 of 41 (68.3%) for oral ketamine, 59 of 102 (57.8%) for intranasal ketamine, 30 of 69 (43.4%) for intranasal midazolam, 7 of 29 (24.1%) for oral midazolam, and 0 of 22 (0%) for oral dexmedetomidine. IND had 9.2% adverse events when used, compared to 16.6% of comparator groups. Bradycardia occurred in 32 of 1484 (2.2%) of the IND group, compared to 0% of IND plus another sedative and 6 of 595 (1%) of non-IND groups. Hypotension was seen less with 18 of 1484 (1.2%) of IND groups compared to non-IND groups which had an occurrence of 9 of 595 (1.5%). In painful procedures, IND provided adequate sedation in 80% compared to 53.3% of patients in the comparator groups. In nonpainful procedures, IND provided 85.6% adequate sedation vs 77.3% in comparator groups. When comparing doses of IND, 2 µg/kg provided adequate sedation in 93% patients vs 67% with 1 µg/kg. Other outcomes such as onset of sedation appeared to be overall shorter in IND groups, at 7 to 31 minutes, vs 7 to 44.2 minutes in comparator groups.

Limitations/Bias:
Sedation scores/adequacy of sedation were subjective and can lead to biased outcome reporting. Application of results broadly affected, as nonstandardized tools to determine adequacy of sedation were used in multiple studies.