

Literature Reviews

Review of Literature on Dexmedetomidine

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The July 2006 issue of *Anesthesia and Analgesia* highlights the use of dexmedetomidine, a selective α -2 receptor agonist, in the pediatric population. This drug has sedative, analgesic and sympatholytic properties that can be utilized for its stress reducing effects in the operative setting, thereby decreasing the anesthetic requirements of volatile agents. It also appears to have a wide safety profile; patients can tolerate a large amount without cardiovascular and respiratory support. Adverse reactions include bradycardia and hypertension. Because of these properties, dexmedetomidine may have an important role in sedation both for outside procedures and in the operating room. At this time, this drug is approved for sedation in mechanically ventilated adult patients. This article reviews the four clinical articles in *Anesthesia and Analgesia* that use dexmedetomidine in pediatric cases as well as two editorials that highlight the controversy surrounding the use of this drug in a non-approved setting (i.e., with pediatric patients)

The first article, *The Use of Dexmedetomidine in Pediatric Cardiac Surgery* (Mukhtar AM, et.al.), is a clinical study that shows how dexmedetomidine attenuates the stress in response in patients undergoing cardiac surgery. In this study, 30 patients, ages 1-6 years, underwent open heart surgery with cardiopulmonary bypass. After being induced with fentanyl, midazolam and pancuronium, and being maintained with isoflurane, the patients were randomized to two groups. One group received a placebo infusion of normal saline, the other group received dexmedetomidine. These infusions were started at the beginning of the case and continued until the end of cardiopulmonary bypass. Heart rate and blood pressure were recorded at various intervals and blood samples for cortisol, epinephrine, norepinephrine and glucose were taken as well. Sodium nitroprusside was given at rewarming to maintain blood pressure at 50-60 mmHg. The results of this study showed that the dexmedetomidine group had significant decreases in mean arterial blood pressure (MAP) and heart rate (HR) compared to the control group. The dexmedetomidine group also had a less rapid rate of increase after sternotomy. The dexmedetomidine group needed less nitroprusside at rewarming. While stress hormone levels increased in both groups, the hormone level rise was higher in the control group. From these results, the authors discussed that using dexmedetomidine in pediatric cardiac surgery decreased HR and MAP due to the sympatholytic effects of dexmedetomidine on the α -2 receptor. While dexmedetomidine does not affect steroidogenesis, it did decrease cortisol levels leading to decrease glucose levels, suggesting that dexmedetomidine may attenuate the neuroendocrine response to stress. The authors noted the limitations of the study included the selection of relatively healthy patients undergoing shorter cardiac surgery. To understand the efficacy and safety of

dexmedetomidine in complex patients,

the authors thought more work needed to be done on complicated patients undergoing complex congenital heart surgery.

The second article, *Dexmedetomidine for Pediatric Sedation for Computed Tomography Imaging Studies* (Mason KP, et.al.), is a prospective study evaluating a pilot program at Children's Hospital Boston that substitutes dexmedetomidine for pentobarbital to sedate patients undergoing a CT scan. The purpose of the change was to decrease the rate of failed sedation and decrease recovery time. After baseline vital signs were recorded, patients received an initial loading dose of 2 ug/kg over 10 minutes. As they became sleepy, their sedation scores were evaluated based on the Ramsay score (see addendum). If the scan went beyond a certain time and the appropriate sedation level was achieved, a maintenance infusion was started at 1 ug/kg/hr. If the patients were not sedated, they received an additional bolus and an infusion was started at 1 ug/kg/hr. After reviewing the data from 62 patients, average age of 2.8 years and weight of 14.6 kg, the investigators found that 16% of patients needed a second bolus and 90% of patients required a maintenance infusion. HR and MAP were 15 % lower from the baseline values. 16% of patients did experience some sinus arrhythmias but remained hemodynamically stable. No changes in respiratory rate, ETCO₂, or O₂ saturation were noted. Adverse reactions were noted to be irritability, agitation and vomiting postoperatively. This study demonstrates the usefulness and safety of dexmedetomidine in sedating pediatric patients for radiology procedures. The disadvantages were the need for full monitoring, the concern for cardiac side effects, and that this drug is not FDA approved in the pediatric population. The major methodological issue with this study as in the previous article was the small sample size and the need for larger numbers to truly gauge the true adverse reaction rate of this drug in children.

The third article, *A Comparison of Sedative, Hemodynamic, and Respiratory Effects of Dexmedetomidine and Propofol in Children Undergoing Magnetic Resonance Imaging* (Koroglu A, et.al.), compared dexmedetomidine and propofol sedation for MRI scans. In this study, 30 patients, ages 1-7 years were randomized to receive either propofol or dexmedetomidine. Patients' preoperative anxiety and vital signs were measured. Patients then received either dexmedetomidine 1 ug/kg over 10 minutes followed by an infusion of 0.5 ug/kg/hr or propofol bolus of 3 mg/kg and an infusion at 100 ug/kg/min. Vital signs were measured and a Ramsay sedation score used to judge the level of sedation. If the patients required more sedation, the infusion rates were increased. If the patient still required more sedation, patients in the dexmedetomidine group got midazolam and the patients in the propofol group had another bolus of propofol. The result showed similar success rates for the sedation with both drugs. Both groups had similar hemodynamic profiles, although dexmedetomidine maintained the MAP at a slightly higher level than propofol. The propofol group did have four patients that had O₂ desaturations below 93% and needed respiratory intervention.

The conclusion of the investigators was that while propofol had a faster rate of induction and recovery, dexmedetomidine better preserved HR, MAP and RR. Therefore dexmedetomidine is another useful drug to use for pediatric sedation.

The fourth article, *Short Duration Large Dose Dexmedetomidine in a Pediatric Patient During Procedural Sedation* (Rosen D, et.al.), is a case report of an overdose of dexmedetomidine. The patient was a 3 year old being sedated for an MRI to evaluate an intrathoracic vascular structure. Because of preoperative agitation, the patient received midazolam and intranasal dexmedetomidine, the dose extrapolated from adult patients. After induction, the patient received a dexmedetomidine infusion of 1 ug/kg/min instead of a 1ug/kg bolus over 10 minutes. A propofol infusion was also started. Once the error was noted, the propofol was continued until the patient appeared to be adequately sedated. The patient had no issues during the MRI. In recovery room, the patient was deeply sedated for 3 hours before being aroused by stimulation. He was fully awake at 4 hours and had no other issues. This report points out that dexmedetomidine even at large doses provides hemodynamic stability. However the patient may remain deeply sedated for a long period of time.

Accompanying these articles are two editorials that comment on the state of clinical research in pediatric anesthesia. The first editorial, *Pediatric Research and Scholarship: Another Gordian Knot* (Tobin JR, et.al), discusses the dilemma of clinical studies in children, as illustrated in the articles. FDA provides many regulations in the development of drug research in children to protect their safety. There is even a 6 month extended patent protection to allow sponsors to perform clinical pediatric trials. However the authors argue that this time frame is not enough for clinical trials to be performed with a return on the sponsor's investment. Researchers are left to fend on their own without adequate funding and clinicians must base drug dosages on incomplete data. The second editorial *Pediatric Drug Development in Anesthesiology: An FDA Perspective* (Schultheis LW), reviews the FDA's role in drug research and the laws in place to encourage pediatric drug research. The authors also encourage anesthesiologists to notify the leadership of their specialty about the drugs where additional information benefits children. These articles and editorials highlight the sorry state of drug development in pediatric patients. A drug like dexmedetomidine has many potential benefits for children

in a wide variety of clinical settings. However, because of the difficulties getting resources for a large scale clinical trial, anesthesiologists are forced to base drug dosages on a small, inadequate amount of data. As a specialty anesthesiologists need to demand that sponsors and the FDA commit to improving the process so that we can provide our patients with the best drugs out there in a safe manner.

Addendum

The Ramsay Score

- 1-anxious, agitated, restless
- 2-awake, cooperative, tranquil
- 3-responds to verbal commands only
- 4-brisk response to loud noise, glabellar tap
- 5-sluggish response to loud noise, glabellar tap
- 6-no response

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