Risk and safety of pediatric sedation/anesthesia for procedures outside the operating room

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Introduction
Sedation and anesthesia outside the operating room remains an area of practice that is in great flux. The trend in the past 10 years continues today – providers (both anesthesiologists and other than anesthesiologists) deliver this care for an ever increasing number of patients with a wide range of disease entities. At the same time, anesthesia providers remain intimately involved in almost all of the systems that deliver this care as the anesthesia department represents the referral service for difficult to manage patients as well as the training and credentialing benchmark for sedation/anesthesia providers of all types. In view of these facts, this review will consider the latest literature on the risk and safety of pediatric sedation/anesthesia for tests and minor procedures utilizing a wide range of sources.

Purpose of review
Sedation and anesthesia outside the operating room represents a rapidly growing field of practice that involves a number of different specialty providers including anesthesiology. The literature surrounding this work is found in a variety of journals – many outside anesthesiology. This review is intended to inform readers about the current status of risk and safety involving sedation/anesthesia for tests and minor procedures utilizing a wide range of sources.

Recent findings
Two large database studies have helped to define the frequency and nature of adverse events in pediatric sedation/anesthesia practice from a multispecialty perspective. A number of papers describing respiratory and hemodynamic aspects of dexmedetomidine sedation have also been published. Finally, a number of studies relating to training sedation providers, reporting of sedation adverse events, sedation for vulnerable populations, and (in particular) ketamine sedation adverse respiratory events have also come to light.

Summary
The latest publications continue to document a relatively low risk to pediatric sedation yet also warn us about the potential adverse events in this field. The results help to define competencies required to deliver pediatric sedation and make this practice even safer. Particularly interesting are new jargon and methodologies for defining adverse events and the use of new methods for training sedation providers.

Keywords
children, dexmedetomidine, pediatrics, procedural sedation, risk, safety

Large database analysis of sedation/anesthesia adverse events outside the operating room
The results of two large database studies have been published in the past 2 years that lend some clarity to the always murky issue of exactly what is the rate and nature of adverse events involving sedation/anesthesia outside the operating room. Both of these studies come from the Pediatric Sedation Research Consortium – a collaborative group of 37 institutions that share information on sedation practice. The first study published in Pediatrics in 2006 evaluated the nature and rate of adverse events among 35,000 sedation encounters [1]. The data evaluated were extensive. To summarize the results, it was found that there were no deaths reported in this database and only one ‘code’ (directly associated with sedation care) and one aspiration episode were reported. On the other hand, approximately one in 400 procedures was associated with stridor, laryngospasm, wheezing, or apnea that could progress to poor outcomes if not...
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managed well. One in every 200 sedations required airway and ventilation interventions ranging from bag–mask ventilation to oral airway placement to emergency intubation. The authors point out that the results do not simply reassure providers that the sedation of children is of low risk, but rather they help to define the core competencies required to deliver this care. In the discussion section, they explain that all the participating institutions have specialty sedation services staffed by anesthesiologists, emergency medicine physicians, intensivists, or hospitalists. As such, these systems likely outperform many sedation/anesthesia programs that operate piecemeal or without a stringent quality improvement process.

A more recent report from the same consortium group reported on 49,836 sedation encounters involving propofol – delivered by the same array of specialists mentioned above [2]. This report was published with the relatively recent (October 2006) statement from the American Society of Anesthesiologists (ASA) in the background that only anesthesiologists should be granted privileges to deliver deep sedation because of the significant risk that patients who receive deep sedation may enter a state of general anesthesia.] During the 3-year collection period, there were two cardiac arrests, four aspiration events, and no deaths among this cohort. Similar to the initial report, this paper goes on to detail the minor adverse events and airway interventions that were required during the study period. One in 65 of these sedation/anesthesia encounters was associated with stridor, laryngospasm, airway obstruction, wheezing, or central apnea. Once again the authors propose that the data do not simply prove the safety of propofol sedation by a broad spectrum of pediatric sedation providers, but rather help us to understand what the performance can look like among a highly selected and diligent group of sedation systems. Critical competencies for sedation with propofol are also suggested based on the adverse events that were recorded in this study.

Dexmedetomidine developments

Reports of dexmedetomidine (DEX) sedation for procedures outside the operating room continue to increase. The safety of this drug for sedation is the focus of many recent investigations [3,4,5,6]. Two papers from Mason et al. [7,8] have shed some light on the issues involved with the use of DEX for radiological procedures. The first of these studies used an observational database to evaluate the safety and effectiveness of this drug as using three different dosing regimens – all of which were considerably higher than the manufacturers’ recommended dose of this drug for sedation (as used in adults) [7]. The authors describe the process by which they determined their dosing regimen, which included progressively increasing the dose of DEX that they employed over time to optimize performance of the drug. The final dosing regimen included a bolus of 3 μg/kg over 10 min followed by a 2 μg/kg/h infusion. A total of 747 consecutive sedations with DEX were evaluated. Their data indicated that the effectiveness of sedation was significantly improved from 91.8 to 97.6% when the higher dose was employed. Although respiratory depression was not an issue for these patients, there was a significant incidence of bradycardia. In the entire cohort, 16.1% had heart rates that fell below age-specific norms; however, only 4% had heart rates that fell more than 20% below the lower normal limits. In several cases, heart rates fell to less than 60 beats per minute for patients less than 1 year of age. During all of these cases, oxygen saturations remained higher than 95% and blood pressure remained in the normal range. No treatment was given. There were no sequelae from bradycardia reported in any of these patients. Although no specific explanation for the cause of the bradycardia was offered in this paper, the authors seem to suggest that this may be expected with DEX at these doses and it may not represent a particularly dangerous event as other parameters appear to be unaffected.

Mason et al. [8] also reported an exaggerated hypertensive response to glycopyrrolate therapy for bradycardia associated with high-dose DEX. This report consists of three case descriptions of patients who experienced bradycardia while receiving high-dose DEX – as described above. In each case, 5 μg/kg of glycopyrrolate was administered resulting in resolution of the bradycardia and a significant increase in blood pressure with reported mean arterial pressures increasing to well over 100 mmHg from baselines in the 60 mmHg range. The authors theorized that this increase was due to increased heart rate in the face of increased systemic vascular resistance from α-2 stimulation in the peripheral blood vessels. The authors suggested that the treatment of bradycardia in the presence of DEX with glycopyrrolate should be avoided.

In order to further evaluate bradycardia associated with DEX, Hammer et al. [9] evaluated 12 children undergoing electrophysiology studies while under standard dose DEX infusions. Sinus node function and atrioventricular node function were depressed in these patients with significant slowing of the heart rates. The authors recommend against the use of this agent for electrophysiology studies or in children with a risk of bradycardia or heart block.

Several other studies have compared the effectiveness and safety of DEX for sedation outside the operating room with other drug options [6,10]. Heard et al. [11] compared a combination of DEX/midazolam with propofol for MRI imaging. Doses employed for DEX were considerably lower (1 μg/kg bolus followed by 0.5 μg/kg/h infusion) than those used by Mason et al. (above). Among
40 randomized patients, the two drug regimens were found to have similar respiratory indices. Heart rates were lower and blood pressures were higher in the DEX cohort – no profound bradycardia was noted. The only difference recorded between the groups was a longer time to awakening in the DEX/midazolam cohort.

**Developmental disabilities and sedation/anesthesia risk**

The added risk associated with developmental disabilities was recently evaluated by Kannikeswaran et al. [12*]. A retrospective analysis was performed to evaluate medications administered and adverse events associated with sedation/anesthesia for MRI scans in children with developmental disabilities compared with normal children. The doses of pentobarbital and fentanyl provided for sedation were not different between these groups, but the incidence of hypoxia was found to be significantly higher at 11.9 vs. 4.9%. The authors suggested a number of possible explanations for their findings that likely have implications for other sedation/anesthesia providers. These include the fact that patients with developmental disabilities (especially severe cerebral palsy) are known to have 40% narrower palates, perhaps placing them at more risk for airway obstruction. In addition, this patient population is known to have a more sensitive response to anesthetics, which could put them at risk for relative oversedation when compared with patients without disabilities.

The issue of sedation for neurologically impaired patients was also investigated by Cortellazzi et al. [13], evaluating a sequential approach to obtaining MRI scans in children with significant neurological deficiencies. In this case, the authors retrospectively reviewed a program in which chloral hydrate was given to obtain MRI scans in 1104 cases. When sedation failed (27 cases), anesthesia with sevoflurane or ketamine was given to obtain the scan. Supplementation was associated with a significantly increased incidence of airway obstruction: 4.6% vs. 2.4% for those who did not receive supplementation. The incidence of other adverse events was not affected. This study is interesting for two reasons. First, it offers an option for obtaining scans in a relatively efficient manner – by providing a ‘rescue’ system for failed oral sedation. It also gives some insight into the incidence (increase) in respiratory problems that can occur when multiple sedation modalities are added together for this difficult population. It is clear that appropriate airway training is critical when adding additional sedation/anesthesia to an existing sedative, even when the result of that sedation has not yielded adequate conditions to obtain an MRI scan.

In another report on the care of this population, Ray and Tobias [14] reported on their retrospective experience with DEX sedation for EEGs in patients with seizures, autism, and/or pervasive developmental delay (PDD). In this case, DEX was given either orally prior to intravenous placement or by intravenous route. Twenty-five of 40 patients required repeat dosing of their DEX, but all eventually completed their studies and none had any adverse respiratory or hemodynamic events.

**Training and testing sedation systems**

From the journal *Academic Emergency Medicine*, Shavit et al. [15*] reported on the adverse event rates associated with sedation performed by specially trained pediatric residents when compared with emergency medicine staff physicians in a large tertiary care center in Israel. One aspect of sedation practice that has not been studied in any depth is the effectiveness of training of sedation providers. This study represents a fledgling effort to document the outcome of a training course in sedation and to validate the content of such a course. In this case, a cohort of pediatric residents was run through a sedation safety training course that included didactic knowledge and hands-on training and then allowed to provide unsupervised sedation for 635 cases. Their performance in terms of the rate of adverse events when similar drugs were used (1.26%) was compared with 349 sedation cases in which sedation was provided by pediatric emergency physicians (3.35%). There was no significant difference in the rate of hypoxia or adverse events between the groups. Although this study (clearly) does not prove that a training course in sedation safety is all that is needed to provide safe sedation, it is important in that it attempts to look at the ability of a safety training course in sedation to have an impact on the care and practice of pediatric sedation. Further delineation of the specific core competencies taught in such a course and the effect on the resultant delivery of sedation will be helpful.

Another study from Israel evaluated the effect of supplemental oxygen on the ability of sedation providers to detect apnea in sedated patients [16*]. The results of this study found that providers detected apnea earlier in a scenario in which supplemental oxygen was not provided – in the absence of end-tidal CO₂ detection. This finding is not surprising but the really unique part of the methodology of this study was the fact that the testing of performance was all done on human patient simulators. Simulators were set up with and without supplemental oxygen and identical apnea scenarios were presented to multiple sedation providers. This study offers a nice example of how human simulators have the advantage of offering a platform in which identical scenarios can be presented to a myriad of different providers with variation of a specific variable over time. The resulting objective assessment of performance is unique in this area of study and deserves consideration for other (perhaps) more critical issues related to pediatric sedation practice.
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Terminology
A particular problem with the study of risk in sedation/anesthesia outside the operating room is the lack of a clear lexicon of terms that clearly describe adverse events involved in this practice. In a paper from the *Annals of Emergency Medicine*, a group of experts in sedation were assembled to develop a consensus-based set of recommendations for standardizing procedural sedation and analgesia terminology [17**]. The goal was to create a uniform reporting mechanism for future studies to facilitate the aggregation and comparison of results. This is an extensive and complex paper that proposes definitions for a wide array of the terminology surrounding sedation based on a thorough review of the literature on topics related to sedation. Many of the proposed definitions are similar to those already in use, but the authors have opted for an innovative approach to some of the most contentious risk-related issues in pediatric sedation. For instance, oxygen desaturation is defined as a drop in oxygen saturation and one or more of a list of interventions aimed at improving oxygenation. The interventions range from tactile stimulation to tracheal intubation. Similar operational definitions are proposed for other events such as apnea, airway obstruction, and laryngospasm. Standardized definitions have the potential to significantly improve the reporting of sedation adverse events. The major potential drawback of this work likely relates to the fact that the experts are dominated by representatives from emergency medicine (with two representatives from pediatric anesthesiology) and the results of this work are only published in the *Journal of the American College of Emergency Physicians*. As sedation is practiced by a variety of medical specialists, ideally, this advance should be shared by other specialties to allow comparison between the work of – for instance – intensive care sedation/anesthesia providers and the work of emergency medicine specialists.

Ketamine and airway risk
The authors of the paper “Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8282 children” endeavor to improve on the previous studies that have evaluated ketamine for procedural sedation/anesthesia [18*]. They propose that previous studies of the drug have been too small to give accurate assessment of the factors related to airway emergencies that can occur when this drug is used. In order to perform this study, the investigators pooled data from 32 emergency department studies and performed multiple logistic regressions to determine which clinical variables would predict airway and respiratory adverse events. Their findings included an overall airway/respiratory adverse event rate of 3.9% with higher incidences in children younger than 2 years of age [odds ratio (OR) 2.0] and older than 13 years (OR 2.72), high intravenous doses (initial dose >2.5 mg/kg or total dose >5 mg/kg) (OR 2.18). Co-administration of an anticholinergic or benzodiazepine was also noted to have a slightly higher incidence. Several common variables that are often thought to add to the risk of ketamine sedation appeared to have no bearing on risk for airway/respiratory adverse events; these include oropharyngeal procedures, ASA status of 3 or greater, or the choice of intravenous vs. intramuscular route of administration.

The study findings are particularly remarkable for the two unexpected findings that patients over 13 years have added risk with ketamine sedation, as did patients who received co-administration of anticholinergic drugs. It should be noted that this is a complex study that suffers from all the difficulties that meta-analyses have including heterogeneity of the studies and outcome variables. Perhaps most importantly for this analysis is the definition of what constituted an ‘adverse event’ in the overall analysis. In this case, desaturation events were lumped with laryngospasm or airway obstruction, even though many would argue that these events have widely different importance and implications for the patients. The authors note that future efforts in this area would benefit from a more focused analysis of fewer variables.

A recent small study evaluated the safety of ketamine in an emergency department and compared adverse event rates with those found with midazolam and propofol [19]. Overall complication rates were similar, however, the majority of events reported with ketamine related to hypertension and rigidity as opposed to hypoxia and airway obstruction events with the other agents. Although not unexpected, the study results reinforce the unique nature of this drug and the fact that expected adverse events are quite different during its use as compared with other agents.

Finally, another single institution study compared oral with intramuscular ketamine for oncology procedures [20]. A single dose of oral ketamine 10 mg/kg combined with midazolam and atropine was found to be as effective and equally well tolerated as (in a prospective randomized methodology) a single 6 mg/kg ketamine dose combined with intramuscular midazolam and atropine. The authors suggested that the painless administration of oral ketamine may be the preferable route for children undergoing procedures in the future.

Conclusion
Sedation/anesthesia for procedures performed outside the operating room remains a dynamic area of research and a constantly changing milieu of specialty providers.
and medications and routes of administration. Anesthesiologists should understand that the current literature reflects the fact that serious injury resulting from sedation in children is rare, but minor adverse events are actually common. Competencies required to provide safe sedation will vary with the drugs used as the adverse events associated with DEX and ketamine are clearly different from those associated with pure sedatives/analgesics. In order to best study and understand the nature of risk and safety in pediatric sedation, we need a common lexicon and definitions for adverse events, and this should be agreed upon among all specialists who deliver this care. Future studies that include large cohorts of sedation patients with standardized adverse event terminology, involving a wide range of drug choices and provider types, will help to further define safest and best practice for the future.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


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