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Options for Intranasal Procedural Sedation and Analgesia in Children

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Providing optimal procedural or pre-induction sedation and analgesia for children remains an elusive goal in many situations. Intravenous administration of these agents is often preferred in order to assure rapid drug delivery, but may not always be possible. In these cases, alternatives include intramuscular, oral, buccal, and intranasal administration. The relatively rapid delivery of drug to the bloodstream and the central nervous system after intranasal administration produces effective sedation with minimal patient discomfort, making it a popular option.[1] The literature describing the efficacy and safety of intranasal sedatives and analgesics in children has grown substantially over the past five years.

Intranasal drug administration has become more widely accepted with the availability of inexpensive atomizers such as the LMA MAD Nasal™ device that places a cone-shaped atomizer at the end of a standard disposable syringe to allow for accurate dose measurement and aerosolization.[2] Compared to dripping in the dose with a syringe, these devices improve drug absorption by delivering the dose to a wider surface area. Concentrated parenteral injections are preferred for intranasal administration, as volumes greater than 1 mL per nostril may saturate the nasal mucosal surface and drain out of the nasal cavity. The primary disadvantage of intranasal drug administration is transient nasal irritation, with some patients also experiencing cough, vocal cord irritation, or laryngospasm.[1]

Fentanyl and Sufentanil

Intranasal fentanyl has been used for the management of acute or procedural pain in children for more than a decade.[3,4] In 2011, Mudd reviewed 12 pediatric observational, placebo-controlled and comparison studies. The author found consistently lower pain scores with intranasal fentanyl when compared to placebo and similar scores when it has been compared to IM or IV morphine.[5] Intranasal fentanyl has been shown to be effective in a variety of settings, including emergency departments (ED), procedural areas, and operating rooms.

In a 2012 study comparing the postoperative analgesia provided by intra-operative administration of intranasal fentanyl (2 mcg/kg) and IV or IM morphine (0.1 mg/kg) during bilateral myringotomy and ventilating tube placement, Hippard and colleagues found that the three options provided equivalent postoperative pain control.[6] The groups had similar rates of complications, time to discharge, and parental satisfaction scores.

Intranasal fentanyl has been found to be effective over a range of ages, from infants as young as 6 months to adolescents.[6,7] Cole and colleagues evaluated pain scores in 46 children between 1 and 3 years of age given intranasal fentanyl for acute pain in the ED.[7] A dose of 1.5 mcg/kg was administered with an atomizer and pain was assessed with the Faces, Legs, Arms, Cry, Consolability (FLACC) scale. The mean FLACC score of 8 at baseline declined to a mean of 2 at 10 minutes ($p < 0.0001$). Pain scores were significantly lower than baseline in 93% of patients at 10 minutes and in 98% at 30 minutes. No serious adverse effects were noted. Mean heart rate and respiratory rate declined after fentanyl administration, but no measurements were below age-related normal values.

Sufentanil has also been used for intranasal sedation and analgesia.[8] It is approximately 5-10 times more potent and twice as lipophilic as fentanyl. Although not as widely studied, sufentanil appears to be an effective alternative to fentanyl and may be better tolerated. Roelofse and colleagues compared combinations of intranasal sufentanil/midazolam and ketamine/midazolam for pre-induction sedation in 50 children between 5-7 years of age. There were no significant differences between the groups in sedation or anxiety, heart rate, blood pressure, or oxygen saturation. The authors reported no cases of respiratory depression.

Midazolam

Intranasal midazolam has been used as a sedative/anxiolytic and an antiepileptic.[1] It has become well accepted as a means of providing

sedation for radiologic imaging and prior to induction of anesthesia, alone or in combination intranasal regimens. In 2012, Baldwa and colleagues compared the effects of intranasal midazolam doses of 0.2 and 0.3 mg/kg as a premedication in 60 children undergoing elective surgery.[9] The two doses were compared for the level of sedation and ease of parental separation. Patients were also graded according to their acceptance of the dose and willingness to have their face mask placed. Overall, acceptance of the intranasal route was rated as good in 23.4% of children, fair in another 43.4%, and poor in 33.4%. There was a significantly higher percentage of patients in the 0.3 mg/kg group who were adequately sedated at 10 minutes (70% versus 40% in the 0.2 mg/kg group, $p = 0.04$). Separation from parents was also rated as easier in the higher dose group, with 66.7% of patients achieving a score of excellent, good, or fair at 10 minutes, compared to only 30% of the children given the lower dose ($p = 0.005$). Transient adverse effects were common, with 60% of children experiencing nasal irritation, 42% having conjunctival congestion, and 30% having increased salivation. There were no cases of oxygen desaturation or bradycardia.

Another recent paper by Filho and colleagues demonstrated the utility of intranasal midazolam for sedation during computed tomography.[10] The authors of this observational study evaluated 58 children (1-40 months of age) receiving a total of 60 scans. The mean initial dose was 0.42 ± 0.03 mg/kg, with a range of 0.37-0.51 mg/kg. Fifteen patients required a second dose. Mean time to adequate sedation was 15.2 ± 9.4 minutes, with a mean time to recovery of 51.1 ± 25.3 minutes. Image quality was rated as excellent in 93.3% of cases, with 98.3% having no imaging artifacts. Only four patients failed to become adequately sedated. Paradoxical agitation occurred in 5% of the patients, with prolonged recovery time and emesis each occurring in 1.7%. Due to the relatively young age of the patients in this study, assessing nasal irritation was difficult, but the authors reported that 28.3% of patients cried during drug administration.

It has been suggested that premedication with lidocaine can reduce the discomfort associated with intranasal midazolam. In a prospective open-label study of 46 children between 5 and 50 months of age, Chiaretti and colleagues used a single puff of lidocaine spray (10 mg) given by the patients' parents to provide a local anesthetic effect immediately before a 0.5 mg/kg intranasal midazolam dose was administered.[11] The mean time to effective sedation was 6.9 ± 2.4 minutes, with a mean duration of 23.1 ± 10.3 minutes. The authors found a high rate of acceptance by the children and favorable ratings for this regimen by both parents and physicians.

Ketamine

Ketamine, a popular choice for procedural sedation in children, can be given by IV, IM, oral, rectal, or intranasal routes. Several studies have described the safety and efficacy of intranasal ketamine in children, including three published within the past year. In the August 2012 issue of *Pediatric Emergency Care*, Tsze and colleagues described their randomized, double-blind, dose-finding study of ketamine for sedation during laceration repair.[12] Twelve patients (1-7 years of age) were randomized to receive 3, 6, or 9 mg/kg intranasal ketamine. The mean duration of sedation produced by the three arms was 42, 36, and 69 minutes, respectively. Only three children, all of whom received a 9 mg/kg dose, were considered to have adequate sedation. Ketamine was well tolerated, with the only reported adverse effect being emesis in one patient. The authors concluded that the higher dose of ketamine was needed to provide optimal dissociative effects.

Hosseini Jahromi and colleagues recently conducted a study comparing intranasal midazolam to intranasal ketamine in 120 children between 2 and 8 years of age.[13] The children were randomized to receive either intranasal midazolam (0.2 mg/kg), intranasal ketamine (either 0.5 mg/kg or 3 mg/kg), or a saline placebo. Anxiety (assessed with the modified Yale preoperative anxiety score) and level of sedation were the primary outcomes. The mean anxiety score was significantly lower in the midazolam group than in either ketamine group or the controls ($p < 0.05$). Ramsay sedation scores were significantly higher in the midazolam group, and higher in the 3 mg/kg ketamine group than in the 0.5 mg/kg ketamine or placebo groups. The results of these two studies suggest that intranasal ketamine doses significantly higher than those used for IV or IM administration may be necessary to produce adequate sedation and anxiolysis in children.

In contrast, Yeaman and colleagues recently reported positive results with a sub-dissociative dose of approximately 1 mg/kg intranasal ketamine in children with limb injuries in the ED.[14] Twenty-eight children between 3 and 13 years of age were included in the study. The mean ketamine dose administered after rounding was 0.84 mg/kg. Patients could be given a second 0.5 mg/kg dose if needed. Each dose was diluted to a volume of 0.5 mL with normal saline and administered as 0.25 mL into each nostril. Upon initial assessment at 15 minutes, 10 children (36%) were given a second dose. The median pain scores using visual analog scales were 74.5 mm at baseline, 30 mm at 30 minutes, and 25 mm at 60 minutes (both $p < 0.001$ compared to baseline). Seventy-one percent of parents were satisfied with their child's analgesia

at 15 and 30 minutes and 83% were satisfied at 60 minutes. Sedation was rated as mild in nearly half the patients at 15 and 30 minutes post dose, but only 2 of the patients were sedated at 60 minutes. The rest were awake and alert. Adverse effects were frequent in this trial, with dizziness reported in 10 children, a bad taste in 8, dysphoria in 4, nausea and sore throat in 3, and amnesia, headache, and emesis/jaw pain in one patient each. All adverse effects were transient and considered mild by the authors.

These three studies show the wide range of intranasal ketamine doses being used in clinical practice. More research is clearly needed to determine the optimal dosing range and to identify patient populations who might require higher ketamine doses to produce adequate sedation or amnesia.

Dexmedetomidine

Over the past five years, dexmedetomidine has become a common option for providing IV sedation and analgesia in children. While most often administered as a continuous infusion in the intensive care unit, dexmedetomidine is increasingly being studied as an alternative to standard agents for intranasal administration. Within the past year alone, four new randomized comparison studies of pediatric intranasal dexmedetomidine have been published, representing work in four different universities in three countries.

In their 2012 study in *Anaesthesia*, Yuen and colleagues randomized 116 children between 1 and 8 years of age to receive an intranasal dexmedetomidine dose of either 1 mcg/kg or 2 mcg/kg as a pre-induction sedative.[15] Adequate sedation at the time of induction was achieved in 53% of the children in the lower dose group versus 66% in the higher dose group ($p = 0.049$). The difference between the two doses was more noticeable in the children between 5 and 8 years of age, where the 2 mcg/kg dose resulted in significantly more patients achieving satisfactory sedation, than in the 1-4 year olds who responded the same to both doses.

Cimen and colleagues enrolled 62 children (2-6 years of age) scheduled to undergo minor elective surgery into a randomized, double-blind trial comparing buccal and intranasal dexmedetomidine as a pre-induction sedative.[16] A 1 mcg/kg dose of dexmedetomidine was given in both groups 45 minutes prior to anesthetic administration. Sedation scores were significantly higher in the intranasal group, beginning at the 10 minutes and continuing until the final assessment at 45 minutes. Ease of parental separation was considered satisfactory in 75.5% of the intranasal group, compared to only 16.2% of the buccal group. Acceptance of face mask placement was also significantly higher (80.6% versus 0, both $p < 0.0001$). There were no differences in heart rate, respiratory rate, or oxygen saturation between groups.

Gyanesh and colleagues at the Global Hospital in Chennai, India, compared intranasal dexmedetomidine and ketamine for procedural sedation in children undergoing an MRI.[17] A total of 150 children between 1 and 10 years of age were randomized to receive either 1 mcg/kg intranasal dexmedetomidine, 5 mg/kg intranasal ketamine, or saline 30 minutes prior to placement of an IV catheter. There were no significant differences in the children's response to administration of the drug. As expected, fewer children in the two treatment groups withdrew or fought against IV placement than in the control group ($p < 0.01$). There was no difference in response between dexmedetomidine and ketamine. The anesthesiologist was satisfied with cannulating conditions in 90.4% of the dexmedetomidine cases, 82.7% of the ketamine cases, and 21.7% of the controls. Rates of parent satisfaction were similar, with 97.3% of the parents of the children given dexmedetomidine, 92.4% of the parents of children given ketamine, and 41.6% of the parents of the controls considering their child to be adequately sedated. There were no significant differences in adverse effects among the groups and no serious events.

The combination of intranasal dexmedetomidine and oral ketamine for premedication prior to induction of anesthesia was recently studied by Jia and colleagues.[18] These authors randomized 160 children between 2 and 6 years of age into one of four groups: 1) 1 mcg/kg intranasal dexmedetomidine with 3 mg/kg oral ketamine, 2) 1 mcg/kg intranasal dexmedetomidine and 5 mg/kg oral ketamine, 3) 2 mcg/kg intranasal dexmedetomidine and 3 mg/kg oral ketamine, and 4) 2 mcg/kg intranasal dexmedetomidine and 5 mg/kg oral ketamine. Overall, 90% of the children accepted their premedication regimen. Onset times were similar among the groups. Patients in group 4 were significantly more sedated than those in group 1 at 30 minutes ($p = 0.036$). Acceptance of IV placement was significantly higher in groups 3 and 4 (84% and 87%, respectively) than in groups 1 and 2 (40% and 54%, $p = 0.001$). The authors suggest that a regimen of 2 mcg/kg intranasal dexmedetomidine and 3 mg/kg oral ketamine may be optimal for providing sedation and anxiolysis in young children prior to surgery.

Studies in Progress

In addition to these recently published studies, there are several studies of intranasal sedation and analgesia currently underway. Barrett and colleagues from the Pediatric Emergency Department at Lady's Children's Hospital in

Dublin are conducting a randomized, double-blind study comparing intranasal fentanyl (1.5 mcg/kg) and IV morphine (0.1 mg/kg) for the treatment of severe sickle cell pain crises.[19] The primary outcome will be pain scores at 10 minutes, with secondary outcomes of pain scores over the first 2 hours after drug administration, the need for rescue analgesia, and the incidence of adverse effects. The results of this study will be the first comparative data on the use of intranasal analgesia in the sickle cell patient population.

The protocol for the Australian Pain in Children – Fentanyl or Ketamine (PICHFORK) study was recently published in *Trials*.[20] The authors of this prospective, randomized, double-blind trial plan to enroll a minimum of 36 children between 3 and 13 years of age with isolated musculoskeletal limb injuries presenting to the Emergency Department. Subjects will be randomized to intranasal fentanyl (1.5 mcg/kg) or intranasal ketamine (1 mg/kg). Outcomes will be pain scores, degree of sedation, patient/family satisfaction, and the presence of adverse effects. This will be the first comparison between these two commonly used drugs.

Summary

Intranasal administration of analgesics and sedatives appears to be a safe and effective alternative in cases where IV access is not available. A variety of agents can be administered intranasally, allowing clinicians to select a drug based on the individual patient's needs and the anticipated length of the procedure. The literature in this area has grown substantially in the past decade and will be further enriched when the results of several ongoing comparison trials become available.

References

1. Wolfe TR, Braude DA. Intranasal medication delivery for children: a brief review and update. Pediatrics 2010;126:532-7.
2. LMA MAD Nasal™ product information. Available at: www.lmana.com/pwpcontrol.php?pwpID=6359 (accessed 8/14/13).
3. Chung S, Lim R, Goldman RD. Intranasal fentanyl versus placebo for pain in children during catheterization for voiding cystourethrography. Pediatr Radiol 2010;40:1236-40.
4. Borland M, Jacobs I, King B, et al. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. Ann Emerg Med 2007;49:335-40.
5. Mudd S. Intranasal fentanyl for pain management in children: a systematic review of the literature. J Pediatr Health Care 2011;25:316-22.
6. Hippard HK, Govindan K, Friedman EM, et al. Postoperative analgesic and behavioral effects of intranasal fentanyl, intravenous morphine, and intramuscular morphine in pediatric patients undergoing bilateral myringotomy and placement of ventilating tubes. Anesth Analg 2012;115:356-63.
7. Cole J, Shepherd M, Young P. Intranasal fentanyl in 1-3-year-olds: a prospective study of the effectiveness of intranasal fentanyl as acute analgesia. Emerg Med Australasia 2009;21:395-400.
8. Roelofse JA, Shipton EA, de la Harpe CJ, et al. Intranasal sufentanil/midazolam versus ketamine/midazolam for analgesia/sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: a prospective, double-blind, randomized comparison. Anesth Prog 2004;51:114-21.
9. Baldwa NM, Padvi AV, Dace NM, et al. Atomised intranasal midazolam spray as premedication in pediatric patients: comparison between two doses of 0.2 and 0.3 mg/kg. J Anesth 2012;26:346-50.
10. Filho EM, de Carvalho WB, Gilio AE, et al. Aerosolized intranasal midazolam for safe and effective sedation for quality computed tomography imaging in infants and children. J Pediatr 2013;E-pub ahead of print.
11. Chiaretti A, Barone G, Rigante D, et al. Intranasal lidocaine and midazolam for procedural sedation in children. Arch Dis Child 2011;96:160-3.
12. Tsze DS, Steele DW, Machan JT, et al. Intranasal ketamine for procedural sedation in pediatric laceration repair: a preliminary report. Pediatr Emerg Care 2012;28:767-70.
13. Hosseini Jahromi SA, Hosseini Valami SM, Adeli N, et al. Comparison of the effects of intranasal midazolam versus different doses of intranasal ketamine on reducing preoperative pediatric anxiety: a prospective randomized clinical trial. J Anesth 2012;26:878-82.
14. Yeaman F, Oakley E, Meek R, et al. Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: a pilot study. Emerg Med Australia 2013;25:161-7.
15. Yuen VM, Hui TW, Irwin MG, et al. A randomized comparison of two intranasal dexmedetomidine doses for premedication in children. Anaesthesia 2012;67:1210-6.
16. Cimen ZS, Hanci A, Sivrikaya GU, et al. Comparison of buccal and nasal dexmedetomidine premedication for pediatric patients. Pediatr Anesth 2013;23:134-8.
17. Gyanesh P, Haldar R, Srivastava D, et al. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial. J Anesth 2013;E-pub ahead of print.
18. Jia JE, Chen JY, Hu X, et al. A randomized study of intranasal dexmedetomidine and oral ketamine for premedication in children. Anaesthesia 2013;E-pub ahead of print.
19. Barrett MJ, Cronin J, Murphy A, et al. Intranasal fentanyl versus intravenous morphine in the emergency department treatment of severe painful sickle cell crises in children: study protocol for a randomized controlled trial. Trials 2012:13:74.
20. Graudins A, Meek R, Egerton-Warburton D, et al. The PICHFORK (pain in children - fentanyl or ketamine) trial comparing the efficacy of intranasal ketamine and fentanyl in the relief of moderate to severe pain in children with limb injuries: study protocol for a randomized controlled trial. Trials 2013;14:208.

Formulary Update

The Pharmacy and Therapeutics Committee did not meet in July.

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