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Commentary

Administration of paediatric intranasal sedation: Need for appropriate formulation & equipment for dispensation

'It has been observed that one's nose is never so happy as when thrust into the affairs of others from which some physiologists have drawn the inference that the nose is devoid of the sense of smell'

–Ambrose Bierce (1842-1914), American short story writer, journalist, poet and civil war veteran.

Bierce's satire in *The Devil's Dictionary,* while outlining functions other than olfaction for one of the five principal human sense organs, failed however, to enlist one of the important pharmacological roles of the nose, as a route for drug administration. Intranasal drug delivery is aimed at a definitive method of bypassing the blood-brain barrier. Because of the direct connection between the central nervous system (CNS) and the nasal cavity, one may go for the intranasal provision of medications. Designated intranasal preparations have emerged as well, to break down enzymatic ions and boost their pharmacological sequelae[1].

Pre-operative anxiety among children is well known due to various reasons, which may depend on the age of the child, previous hospital experiences and associated cognitive and behavioural disorders[2]. Parental separation, fear of painful procedures and previous traumatic experiences are some of the reasons[3]. It can be stressful for the parents and anaesthesiologists alike. The overall distressing experience can not only have a negative impact on the perioperative course but also can lead to an increased risk of developing emergence delirium and can increase analgesic requirements. It can also produce behavioural changes such as aggression, worsening anxiety, sleep disturbances, enuresis and eating disorders[4]. To prevent these adverse events, it is imperative to take necessary measures, some of which include, but are not limited to smooth parental separation, smooth induction of anaesthesia, blunting the stress response and providing adequate analgesia with regional analgesic techniques.

There are various ways to ensure smooth parental separation and acceptance of procedures, most of which mainly depend on the age of the child. Infants before experiencing separation anxiety, that is around 6-9 months of age, are easier to manage as they mostly calm down on rocking, being held and comforted by caregivers, as long as they are not kept fasted for prolonged hours. Children of 5-12 yr of age may understand the need for procedures, and hence, simple explanation, reassurance and the familiarity of staff and place may reduce anxiety to an extent, along with distraction and play. The most difficult age group is toddlers and pre-schoolers around 1-4 yr of age, as separation anxiety is more in this group[5]. Rationalization and reasoning are not yet well developed by such age to an extent that kids in this age group can comprehend things. This is where sedative pre-medication plays a significant role in smoothening the entire process for everyone involved.

Some of the commonly used pre-medication drugs in the paediatric population include benzodiazepines (midazolam), alpha-2 adrenoceptor agonists (dexmedetomidine and clonidine), NMDA-receptor antagonists (ketamine) and opioids (fentanyl)[3,6]. Each has both advantages and disadvantages. The choice, therefore, depends on the drug and the formulation available, the degree of cooperation of the child, the experience of the anaesthesiologist and contraindications if any. Various routes can be chosen for administering these sedative pre-medication agents, but the most commonly used and accepted ones are oral, nasal, intramuscular, intravenous (IV) (easier if IV cannula is already in place) and rectal[3].

Intranasal administration of pre-medication, such as midazolam, dexmedetomidine and ketamine, has

become common practice in recent times owing to the ease of administration, atraumatic dispensation and higher bioavailability due to bypass of first-pass metabolism and increased vascularity of nasal mucosa[5,7]. Although nasal irritation and burning are reported, tolerance is still better via this route. Several studies have compared different routes and different medications, comparing levels of sedation, ease of separation, facilitation of smooth induction and incidence of adverse effects. Midazolam provides anxiolysis, sedation and anterograde amnesia. Dexmedetomidine has sedative, analgesic and sympatholytic properties[8]. Unlike other sedative agents, this α-2 agonist preserves respiratory function, thereby providing arousable sedation. The major drawback of this drug, however, is bradycardia and hypotension. The majority of the inhalational and IV anaesthetic agents act via gamma-aminobutyric acid (GABA) receptors to induce and maintain the reversible loss of consciousness[9]. The action of dexmedetomidine is, however, independent of the GABA receptor pathway, and thereby, it helps in decreasing the consumption of intra-operative anaesthetic agents and analgesics and also prevents emergence delirium in children[4,6] .

A study published in this issue[10] has compared the efficacy of intranasal dexmedetomidine-fentanyl with intranasal midazolam-fentanyl combinations in children aged 3-8 yr undergoing elective procedures and has concluded that both combinations effectively reduce anxiety, aiding ease of separation and providing satisfactory sedation, with the dexmedetomidine combination being slightly superior in this regard and, therefore, lending itself to regular use for this purpose. Another significant finding in this study is that the post-operative pain scores were significantly reduced in the group using dexmedetomidine, which may be attributed to its inherent analgesic properties, adding to its advantage as a sedative–anxiolytic. There are some limitations of the study, however, as the drug preparations used were approved for IV and not for intranasal use and, therefore, may be considered 'off-label' administration of these drugs. Furthermore, the time of onset and peak effect of the drug combinations could have also been noted. The sample size estimate was not based on any previous studies and was calculated based on assumptions, hence the interpretation of the statistical significance of the results requires caution. It has been suggested that sedative doses of midazolam (0.5 mg/kg per oral route, 0.05 mg/kg IV route and 0.2 mg/kg intranasal route) may calm the child down and smooth parental separation[11]. However, the child may not allow the anaesthesiologist to hold the mask for inhalational induction or may not allow the IV line to be placed. In this study, as fentanyl was administered intranasally along with midazolam or dexmedetomidine in either group, children might have allowed placement of the IV line. However, since most of the children were well sedated in both the groups as mentioned by the authors, they could have been induced with an inhalational agent, and mask acceptance could have been studied as a parameter instead of a response to venepuncture. Probably that would have been ethically more appropriate in a population group that is generally considered vulnerable in the context of clinical trials.

Further, the study drugs were administered via a syringe. Administration of intranasal drugs via the syringe tips may not disperse the drug formulation uniformly over the nasal mucosa. The use of an appropriate device such as the LMA® mucosal atomizer device (MAD) would probably have delivered the intranasal medication much better. It is also worth mentioning that the US Food and Drug Administration (FDA) has issued a black box warning for utilizing succinylcholine in children and therefore administration of such drug as part of the anaesthetic protocol, when alternatives could easily have been opted for, is rather perplexing[12,13]. The mean peak plasma concentration of dexmedetomidine (C_{max}) to achieve acceptable sedation is 0.54±0.17 ng/cc which was achieved by administration of 2-3 μg/kg of dexmedetomidine intranasally in some studies[7]. The time to achieve this maximal concentration was around 30-45 min in children[3,7]. On the contrary, within 20 min of administration of 1 μg/kg of intranasal dexmedetomidine, children were sedated well and parental separation was also smooth in this study[10]. This could represent the additional sedative effect of fentanyl.

Conventionally, drug applications via the nasal route may be formulated as solutions, suspensions, gels, emulsions and powders. Although convenient, these traditional formulations have some issues, including low-dose fidelity, large particle size, greater viscosity and instability of the drug preparation[14]. To upgrade paediatric acceptance, different other possible drug preparations and alternate dispensation routes should be explored. Oral and injectable routes of administration provide fairly well-countenanced treatment but are not realizable for all children. Two

salient aspects, lipophilicity (log P) and dissociation constant (pKa), would influence nasal administration of drugs most. Owing to these characteristics, novel means of administration of sedatives based on unique and innovative preparations, involving nanogels, nanostructured lipid, liposome nanoparticles and nanoemulsions/microemulsion, are worth surveying as drug administration approaches for dispensation through the nasal route[15-17]. Hopefully, drug formulations can be made for usage via the intranasal route and such drugs should be palatable as some amount of drug will enter the oropharynx.

It is worth mentioning that streamlined and innovative intranasal medication administration apparatuses employed for unimpeded movement of medications from the nasal cavity to the CNS are a salient scheme for the furtherance of paediatric pre-medication administration, which helps sedative agents to be shifted to their sites of action through the olfactory/trigeminal pathway[14]. Several apparatuses, involving droppers, syringes, pressurized metered-dose inhalers, breath powered bi-directional nasal devices and pressurized olfactory delivery devices, have been ratified in medical therapeutics and have been designated as apparatuses for delivering liquid, powder and semisolid preparations[18,19]. The appropriate dispensation method is dictated by the form of preparation of the medication. Powder preparations typically adhere to the mucosa of the nasal cavity before they are removed. Administration of liquid preparations is the oldest, most economic and most painless modus operandi[14]. Nasal sprays in vogue disperse much easily and coat the olfactory area. Sprays strew the nasal mucosa with the aid of nasal mucociliary eviction. Intranasal could be an appropriate route of administration of sedative pre-medication to children, provided the appropriate device (such as the LMA® MAD nasal) is used to deliver the drug, at the appropriate dosage, providing an appropriate time for the drug to reach its peak sedative effect.

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Satyen Parida* & Muthapillai Senthilnathan
Department of Anaesthesiology & Critical Care,
Jawarlal Institute of Postgraduate Medical Education and Research, Puducherry 605 006, India
**For correspondence*:
jipmersatyen@gmail.com

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