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Intranasal premedication: special consideration in children

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ABSTRACT

Introduction: Surgery in special population such as children may lead to emotional and physical stress. Premedication use may be beneficial in children anesthesia to reduce emotional stress and anxiety but still to be used in special consideration with adjustment dose. Intranasal premedication provides a broad effect of sedation and anti-anxiety and maybe produce a beneficial effect in child anesthesia.

Aim: This study aimed to provide an overview regarding intranasal drugs and also intranasal premedication function in children

Conclusion: The intranasal application of pre-anesthetic drugs is the preferred route of administration and is an effective way to provide sedatives to children.

Keywords: premedication, child, intranasal.

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INTRODUCTION

Surgery and anesthesia induce considerable emotional stress especially in children. The consequences of this stress may remain long after the hospital experience has passed, including prolonged night terrors, negativism, a variety of phobias, hysterical reactions and anxiety reactions. Administration of preanesthetic medication may reduce the risks of adverse psychological and physiological sequela of induction of anesthesia in a distressed child. Premedication may be administered orally, intramuscularly, intravenously, rectally, nasally or sublingually. Although most of these routes are effective and reliable, each has drawbacks as well.¹

The major objectives of preanesthetic medication are to decrease the stress response with preservation of hemodynamic parameters, facilitate anesthesia induction and produce amnesia. The child's age, body weight, drug history, allergic status and underlying medical or surgical conditions are factors to be taken into consideration before administration of premedication. In most cases, medications administered without a needle are more pleasant for children, the family and the care team. Oral premedication does not increase the risk of aspiration pneumonia.²

Among the different results that may be achieved with premedication such as amnesia, optimization of preoperative conditions and prevention of physiological stress, the primary aim of children is anxiolysis. Almost 50% of children show signs of significant preoperative fear and anxiety. It has been reported that there are correlations between

heart rate, blood pressure, and behavioral ratings of anxiety. To alleviate physiological and psychological effects of preoperative anxiety in children, most anesthesiologists use either parental presence or sedative premedication, since separation from parents and induction of anesthesia are considered the most perioperative stress inducing phases. Both approaches are considered appropriate choice of interventions. Anesthesiologists who allow parental presence during induction of anesthesia use sedative premedication least frequently, and vice versa.²

The intranasal route is a reliable way to administer preanesthetics and sedatives especially in children and is a relatively easy noninvasive route with rapid onset of action and high bioavailability comparable to that of IV administration because of bypassing the first pass hepatic metabolism and the high vascularity of the airway mucosa. Furthermore, it has the advantage of well tolerability, not requiring patient cooperation as would be in the case for drug swallowing or sublingual retention and does not have pungency or an unpleasant taste.³

PREMEDICATION

Premedication refers to the administration of medication before the induction of anesthesia. These medications are neither part of the surgical patient's usual medical regimen nor are they part of the anesthetic.

Purposes of premedication

The general objectives of premedication are as follows: (1) to make well-rested patient, making

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them easier to handle and reduce catecholamine release, (2) for muscle relaxation and immobilization and hyporeflexion, (c) to give analgesia (pain relief), (d) to obtain safe induction of anesthesia, to obtain a slow and safe induction of anesthesia, anesthetic stage from anesthetic agents can be reduced.

To prevent “vagal inhibition” and decreasing secretion induced by chloroform or ether, atropine was once used before the anesthesia. Other than atropine, morphine had also been used to reduce reflex irritability of patients and decrease the amount of ether requirement. Nowadays, the main purpose of premedication is no longer to prevent radical movement or reduce secretion of patients but to allay patient fears and lessen patient anxiety.⁴

In the literature, other purposes of anesthetic premedication, as follows: (1) to prevent postoperative pain, (2) prevent postoperative nausea and vomiting, (3) decrease perioperative shivering, (4) decrease postoperative pruritus, (5) decrease gastric secretions, (6) prevent allergic reactions, (7) suppress reflex responses to surgical stimuli, and (8) decrease anesthetic requirement for the surgical procedure.⁴

Reducing postoperative pain

Refer to experimental findings of Woolf and Chong in 1993 about the concept of preemptive analgesia, a concept of delivering an analgesic regimen before the surgical stimulus to reduce the severity and duration of postoperative pain, the central nervous system will be hypersensitized after peripheral tissue injury. The functions of preemptive analgesia include: (1) decreasing acute postoperative pain after peripheral nerve damage and tissue injury; (2) preventing central neuron sensitization; and to inhibit the development of chronic postsurgical pain (CPSP).⁵

In 2005, Ong et al published systematic review paper, which analyzed 3261 patients from 66 randomized controlled trials between 1989 and 2003: 17 trials on systemic NSAIDs, seven trials on systemic NMDA receptor antagonists, eight trials on systemic opioids, 19 trials on epidural local anesthetics and opioids, and 15 trials on wound infiltration or peripheral nerve block. The primary outcome measurements were pain intensity, supplemental postoperative analgesic requirements, and time to first rescue analgesic. From the experiment, they concluded that although preemptive epidural analgesia resulted in consistent improvements in all three outcome measures, preemptive systemic NSAIDs and local wound infiltration both decreased analgesic consumption and delayed time first to rescue analgesic, but had no impact on pain scores.⁶

Decreasing anxiety

In general, anesthesia preparation begins with psychological or mental preparation for patients who will be given anesthesia. Operation is a treatment that causes anxiety. Anxiety is a signal that awakens and warns of a threat that threatens and allows a person to take action to overcome a threat. Anxiety is one of the most stressful emotions felt by many people who will undergo surgery. Preoperative anxiety can occur in as high as 80% of surgical patients. Two vulnerable groups of patients are females and children.³

Both psychological and pharmacological approaches are effective in decreasing preoperative anxiety. Midazolam has been proved to be effective in reducing the preoperative anxiety level in many studies. It will not delay discharge from the recovery room in outpatient surgery. A study conducted by Matana et al. in 2013 suggested administration of Midazolam 0.05 mg/kg BW IV as a premedication can show a decrease in the level of patient's anxiety that can be seen from significant blood pressure reduction but no significant decrease in pulse rate. Except for midazolam, α_2 -agonists, antidepressants, and anticonvulsants are all effective in reducing the preoperative anxiety level.⁷

Preventing Chronic Postsurgical Pain (CPSP)

Chronic postsurgical pain (CPSP) refers to a pain persisting for >3 months after surgery. The highest incidence of chronic pain after surgery is observed in patients undergoing amputation (50-85%), followed by those undergoing cardiac surgery (30-55%), mastectomy (20-50%), and thoracotomy (10-65%). The incidence of CPSP for the minor operation such as hernia repair up to 5-30%. The main mechanism that plays an important role in the development of CPSP is nerve damages and central sensitization.⁸

Preventing Post Operative Nausea and Vomiting (PONV)

About one-third of surgical patients who receive general anesthesia consisting of inhalational anesthetics and opioids experience PONV. The mechanism of PONV is complicated, and several kinds of receptors and their mediators have been implicated in PONV: (1) serotonin type 3 (5-HT₃) receptor; (2) dopamine type 2 receptor; (3) histamine type 1 receptor; (4) muscarinic cholinergic type 1 receptor; (5) steroid receptor; and (6) neurokinin type 1 (NK1) receptor.⁹

Decreasing Perioperative Shivering

Post-anesthetic shivering has been reported in 40-64% of patients (average 55%) with no

prophylaxis. To reduce the perioperative shivering, in the literatures categorized several classes drugs, as follows: (1) opioid receptor agonists or antagonists; (2) other centrally acting analgesics such as tramadol and nefopam; (3) α_2 -receptor agonists such as clonidine and dexmedetomidine; (4) cholinesterase inhibitors such as physostigmine and anticholinergic: atropine; (5) central nervous stimulants such as methylphenidate; (6) N-methyl-D-aspartate receptor antagonists such as ketamine and magnesium sulfate; (7) antiserotonergic agents such as ondansetron, granisetron, dolasetron, and urapidil; (8) γ -aminobutyric acid receptor agonists such as midazolam and propofol; (9) sodium channel blockers such as lidocaine; (10) benzodiazepine receptor antagonists such as flumazenil; and (11) anti-inflammatory agents such as dexamethasone.³

Decreasing Postoperative Pruritus

Pruritus is the most common side effect of neuraxial opioids, with an incidence varying from 30% to 100%. Although the exact mechanisms still understood, it is believed that activation of m-opioid receptors in dorsal horn neurons or the "itch center" of the medulla by cephalad migration of neuraxial opioids is a major reason. Modulation of the serotonergic pathways by interactions of opioid and 5-HT₃ receptors and involvement of prostaglandins are also important in neuraxial opioid-induced pruritus. Pharmacological strategies to prevent or treat such an event include the following: 5-HT₃ receptor antagonists, opioid antagonists, antihistamines, NSAIDs, and droperidol.¹⁰

Decreasing Gastric Secretions

Nowadays, aspiration pneumonitis caused by regurgitated gastric juice from the full stomach of inadequately fasting patients or the stomach of a parturient is a challenge for anesthesiologists. To prevent the aspiration includes fasting as a general preparation for patients who undergo surgery, gastric decompression, acceleration of emptying, and application of the technique of rapid sequence intubation along with Sellick's maneuver. Besides that, premedication that can inhibit gastric juice secretion and reduce gastric juice volume and acidity, such as H₂-receptor antagonists (H₂RAs) or proton pump inhibitors (PPIs).³

Many clinical trials have compared the efficacy of H₂RAs with that of PPIs regarding reducing gastric juice volume and acidity. Clark et al¹¹ analyzed 913 patients in seven trials comparing the effects of ranitidine with that of PPIs on gastric secretion. The outcomes of their analysis suggested that ranitidine is more effective than PPIs in reducing gastric juice volume and acidity. Ranitidine can

decrease the volume of gastric aspirates by an average of 0.22 mg/kg (95% CI 0.04-0.41) and increase gastric PH by an average of 0.85 pH unit (95% CI 1.14-0.28).

INTRANASAL PREMEDICATION

The intranasal route is a reliable way to administer preanesthetics and sedatives especially in children and is a relatively easy noninvasive route with rapid onset of action and high bioavailability comparable to that of IV administration because of bypassing the first pass hepatic metabolism and the high vascularity of the airway mucosa.^[4] Furthermore, it has the advantage of good tolerability, not requiring patient cooperation as would be in the case for drug swallowing or sublingual retention and does not have pungency or an unpleasant taste.³

Midazolam

Midazolam belongs to benzodiazepine group that widely used as anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and antegrade amnesic. γ -Aminobutyric acid (GABA) acts as an inhibitory neurotransmitter when bound to the GABA_A receptor, which distributed in the central and peripheral nervous system.

In intranasal route, the bioavailability ranges from 50-83%. It can be administered orally, nasally, rectally, IV or IM. In a randomized, double-blind, placebo control study, Shapiro et al¹² showed that midazolam spray offers relief to children anxious about minor medical procedures, such as insertion of a needle in a subcutaneously implanted intravenous port, venous blood sampling and venous cannulation. A double-blind, randomized, controlled trial conducted by Rakaf et al¹³ in 2011 reported a success rate of 91% to 100% for completing dental procedures following intranasal midazolam administration. The dose of intranasal midazolam used in the different studies range between 0.2 mg/kg and 0.4 mg/kg or 0.5 mg/kg¹¹⁻¹⁵. The most common adverse effects reported following IN midazolam are burning or irritation in the nose and a bitter taste in the mouth. It can determine respiratory and circulatory depression, but these side effects are unlikely when midazolam is used as a single drug, while they increase when it is used with opioids or other sedatives.

Nitrous Oxide and Fentanyl

Seith et al. administered a continuous flow of nitrous oxide of 50 to 70% via a full-face mask in association with a pre-calculated dose of 1.5 μ g/kg of intranasal fentanyl that was administered through MAD. Nitrous oxide alone agent has been associated with higher levels of emesis; instead, according to

Seith et al., the association with intranasal fentanyl reduces the incidence of vomiting. Fentanyl is an opiate analgesic with the most evidence to support intranasal route. It is mostly used for acute pain management like orthopedic fractures or burns because it controls at relatively high doses the pain. Its usage in pediatric patients has shown comparable effectiveness with the IV administration.¹⁴

Dexmedetomidine

Dexmedetomidine is a selective group of α_2 -adrenoceptor agonists commonly used as anxiolytic, sedative and analgesic. Initially dexmedetomidine is used intravenously (IV) as sedation for adult patients in the Intensive Care Unit (ICU). In 2018, its use is growing so that it is used in patients who are not intubated.

Dexmedetomidine received approval from the Food and Drug Administration (FDA) in the United States in 1992 as a short-term (use <24 hours) sedative in the ICU. Dexmedetomidine has an excellent sedative, analgesic and anxiolytic effect when viewed regarding safety. These compounds cause minimal respiratory depression side effects at sedative and anxiolytic doses, which leads to an increase in popularity in anesthesia for the pediatric and intensive care age groups.¹⁵

The mechanism of action of Dexmedetomidine is unique and different from sedative agents which are currently widely used. α_2 -adrenoceptors are found in various locations in the central nervous system. However, the highest density of α_2 receptors is found in the locus Cereleus, a noradrenergic nucleus that is dominant in the brain stem and an important modulator of alert ability. Presynaptic activation of α_2 -A adrenoceptors at the Cereleus locus inhibits norepinephrine release and results in sedative and hypnotic effects. Also, the locus of Cereleus is the original location of the descending pathway of medullary noradrenergic, which is known as an important modulator of nociceptive neurotransmission.¹⁵

The α_2 -adrenoceptors stimulation in this area will minimize the appearance of pain signals that produce analgesic effects. Postsynaptic activation of α_2 -adrenoceptors in the central nervous system decreases sympathetic activity leading to hypotension and bradycardia. Also, activation of α_2 -adrenoceptors in the central nervous system can trigger cardio-vagal activity. When combined, these effects can produce analgesia, sedation, and anxiolytic. At the spinal cord level, the stimulation of α_2 -receptors in the substantia gelatinosa in the dorsal column leads to inhibition of the activity of nociceptive neurons and inhibition of substance release P.¹⁵ α_2 -adrenoceptors located at the nerve

endings may also have a role in the analgesic mechanism of α_2 agonists by preventing norepinephrine release. The spinal mechanism is the main analgesic mechanism Dexmedetomidine has although there is also clear evidence for supraspinal and peripheral mechanisms.¹⁶

α_2 -receptors are located in blood vessels where they can mediate vasoconstriction, and in the sympathetic terminal, where they act to inhibit norepinephrine release. Responses to α_2 -adrenoceptors activation in other locations include vascular contractions and other smooth muscles, decreases salivary production, decreases intestinal motility in the gastrointestinal tract, inhibits renin enzyme release, increases glomerular filtration rate, and increases sodium and water secretion in the kidneys, decreases insulin release from the pancreas, decreases intraocular pressure, reduces platelet aggregation.¹⁷

In one study wanted to find out which dose of intranasal Dexmedetomidine was more optimal, 1 $\mu\text{g}/\text{kg}$ or 2 $\mu\text{g}/\text{kg}$. The results obtained are the use of DXE intranasally with a dose of 2 $\mu\text{g}/\text{kg}$ shows better results than 1 $\mu\text{g}/\text{kg}$, this is seen from the parameters of sedation score and behavior score, intraoperative hemodynamic stability, and postoperative recovery.¹⁷

Clonidine

Clonidine hydrochloride is an imidazoline compound with the chemical name 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. Clonidine, a partial α_2 -agonist (same group with Dexmedetomidine) was characterized by Wolf et al. in 1962 and was first tested as a nasal decongestant due to its α_1 -stimulating effects and vasoconstrictive properties. But now, its sedative, hypotensive and bradycardic effects were noted. Its mechanism of action and effects on adrenergic receptors was studied in the late 1960s and early 1970s and became after that primarily used as an antihypertensive drug. Only minor adverse events as dry mouth and sedation were seen in patients, during the initial period of treatment. Clonidine reduces heart rate modestly, thus, symptomatic bradycardia or orthostatic hypotension are only observed infrequently.¹⁸

Clonidine was introduced for premedication in children in the 1990s. Contrary to all other pharmacologic alternatives clonidine does not involve mental clouding but instead induce adequate preoperative sedation that mimics ordinary tiredness and sleep, and has no clinically relevant impact on memory or respiratory drive. The use of clonidine as premedication has recently been proven to be superior to benzodiazepines in a meta-analysis.¹⁸

SPECIAL CONSIDERATION FOR CHILDREN

In pediatric anesthesia, anxiety is still a challenge for anesthesiologist. Anxiety during pre-surgery can vary in various forms. In accordance with age, these forms of anxiety can be verbal or behavioral. Crying, agitation, urinary retention, deep breathing, unwillingness to talk, are forms of child anxiety. This anxiety can reach its peak when induction of anesthesia. Anxiety and fear in children will increase catecholamine levels and cause tachycardia, hypertension, tachypnea and result in distress in finding intravenous pathways and separating the child from parents in anesthetic induction.

Management of anesthesia in pediatrics is slightly different compared to adults. This is because there are fundamental differences between children and adults, including differences in anatomy, physiology, pharmacological and psychological responses in addition to different surgical procedures in children. Pediatric anesthesia is anesthesia in patients under 12 years of age, which is divided into 3 (three) age groups, namely 1) neonates 2) infants aged <3 years. 3) children aged > 3 years. Several stages of pediatric anesthesia such as evaluation, pre-surgical preparation, and premedication-induction stages are the most stages determine the success of the anesthesia action we will do. The progress of each stage well will determine the next stage. Although there are fundamental differences, the main principles of anesthesia are: vigilance, safety, comfort,

and careful attention to both children and adults are the same.

The challenge of pediatric anesthesia in the operating room (OR) is to minimize distress for children and to facilitate induction of anesthesia. This is done by administering sedatives before being transferred to the operating room. Deep sedation to general anesthesia that is needed during the operation to ensure the child does not move and the reflex becomes dull to painful stimuli.³ Pre-anesthesia drugs in children are provided to reduce anxiety and psychological trauma and also to facilitate induction of anesthesia without delaying recovery. Some drugs have been tried to find the right sedative and the best route for administering these drugs to children. Therefore, the use of drugs as premedication is very important especially for children, and the proper non-traumatic administration routes are needed, so doesn't add extra stress to children.³

The intranasal route is a reliable way to manage pre-anesthetics and sedatives for children and is a relatively easy noninvasive route with rapid onset of work and high bioavailability comparable to IV administration because it passes through liver metabolism that is believed to reduce sedative and vascularization effects high on the mucosal airway so that absorption becomes better. Also, the drug has the advantage of good tolerability, does not require patient collaboration as well as in cases of drug ingestion or sublingual retention and does not provide an unpleasant sensation.¹⁹

The intranasal application of pre-anesthetic drugs is the preferred route of administration and is an effective way to offer sedatives to children. The intranasal route does not require collaboration, is comfortable, is not invasive, is well tolerated, and the child will not feel an unpleasant sensation. Wolfe and Braude said that intranasal drug administration is a noninvasive, painless, fast way to give a drug premedication, with rapid onset of work because drugs can access the systemic circulation due to high vascularization of the subepithelial surface of the nasal cavity. Also, intranasal routes can penetrate the blood-brain barrier and reach the central nervous system directly and avoid hepatic metabolism.^{20,21}

Therapeutic levels of sedatives can be reached via intranasal administration due to the rich vascular plexus cavity which communicates with the subarachnoid space via the olfactory nerve. In the recent past many authors preferred IN midazolam administer by drop instillation; nowadays many studies investigate new methods such as the use of spray devices. A mucosal atomizer device (MAD) delivers drug via a fine spray over a broad surface area in the nasal cavity (Figure 1). It also reduces sneezing and coughing compared to other devices.¹⁴



Figure 1 By using MAD, the drug is delivered via a fine spray over a broad surface area in the nasal cavity, favoring its absorption

CONCLUSION

The intranasal application of pre-anesthetic drugs is the preferred route of administration and is an effective way to offer sedatives to children. The intranasal route does not require collaboration, is comfortable, is not invasive, is well tolerated, and the child will not feel an unpleasant sensation.

CONFLICT OF INTEREST

Author declare there is no conflict of interest regarding all aspect in this review.

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