Comparison of Atomised Sublingual Dexmedetomidine and Oral Midazolam as Preanaesthetic Medication in Children - A Prospective, Double Blind, Randomised Control Trial

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ABSTRACT

BACKGROUND
Pre-operative anxiety is common in children and its relief is an important concern for the anaesthesiologist. Oral midazolam has good sedative and anxiolytic properties. Dexmedetomidine, an alpha-2 agonist, produces sedation like natural sleep, in addition to having analgesic, anxiolytic and anaesthetic-sparing properties, making it a near ideal sedative. Alleviating this anxiety using minimally invasive and painless routes for sedative drugs is of paramount importance. The purpose of this study was to compare the sedation, child-parent separation, and mask acceptance between sublingual atomised dexmedetomidine and oral midazolam, along with the haemodynamic changes associated with these drugs.

METHODS
This prospective, double-blind, randomised control trial was conducted in a tertiary hospital setting. Using computer-generated randomisation, sixty paediatric patients were divided into one of two groups. Group - D received sublingual dexmedetomidine 1.5 µg/kg using a mucosal atomisation device, and Group - M, oral midazolam 0.5 mg/kg, 45 minutes before anaesthetic induction. Sedation status, child-parent separation, mask acceptance scores, haemodynamics and oxygen saturation were measured at baseline and every 15 minutes till induction. Quantitative data were compared with student’s t-test and repeated measures analysis of variance (ANOVA), and qualitative data using chi-square test.

RESULTS
Demographic data were comparable between the two groups. Children in Group - D were significantly more sedated (P < 0.0001), with lower heart rate at 30 and 45 minutes (P = 0.003, < 0.0001 respectively) than Group - M. However, mask acceptance score was significantly better (P = 0.007) in Group - M. Child-parent separation score was comparable.

CONCLUSIONS
Atomised sublingual dexmedetomidine produced significantly greater sedation and low-normal heart rate, but poorer mask acceptance than with oral midazolam. Child-parent separation was comparable. We conclude that sublingual atomised dexmedetomidine 1.5 µg/kg, is not a suitable alternative to oral midazolam 0.5 mg/kg for paediatric premedication.

KEY WORDS
Anaesthesia, Dexmedetomidine, Midazolam, Anti-Anxiety Agents, Premedication, Paediatric
BACKGROUND

One of the biggest challenges for a paediatric anaesthesiologist is relieving the preoperative anxiety in the child. Dealing with an uncooperative or apprehensive child is distressing for the parent and health-care worker as well. In addition, the stress of a turbulent induction can lead to post-operative behavioural changes and can have a negative psychological impact on the child. In children, stress of hospitalization has been attributed to five general fears: fear of separation from their parents, fear of the strange hospital environment, fear of painful procedures, fear of the operation itself, or fear of anaesthesia. A lack of understanding about the need of surgery and nature of illness also contributes to this picture. It can be challenging for the anaesthesiologist to rightly identify children with significant anxiety. Alleviating these fears is an important concern for a stable anaesthetic course. Premedication is commonly used to decrease paediatric preoperative anxiety, to aid in separation of child from parent and to promote acceptance of mask at induction.

There are several methods available to decrease preoperative anxiety, including non-pharmacological and pharmacological methods. Non-pharmacological methods include play therapy and counselling prior to surgery. The ideal premedication in children should be acceptable, have an atraumatic route of administration, rapid and reliable in onset, with minimal side effects and rapid elimination. Oral and transmucosal route is readily acceptable for premedication in the paediatric population as it does not require any painful procedure. Midazolam, a γ-aminobutyric acid (GABA) receptor inhibitor, is one of the most commonly used sedative drugs for premedication in children. It is a water-soluble benzodiazepine with quick onset and short duration of action. It provides effective sedation, analgesia, anti-emetic and varying degrees of anterograde amnesia. It is safe and effective both at separation and induction of anaesthesia. Dexametomidine, a highly selective α2-adrenoceptor agonist, possesses sedative, analgesic, sympatholytic, anaesthetic-sparing, and haemodynamic-stabilising properties, lacks respiratory depression, making it a useful and safe adjunct in diverse clinical practice. Additionally, it is a tasteless and odourless drug, making it a near ideal sedative. Oral bioavailability of dexametomidine is very poor, owing to an extensive first-pass metabolism. However, bioavailability of dexametomidine when given sublingually is high, thus making it an attractive option for paediatric sedation.

Oral or transmucosal routes of premedication are readily acceptable for premedication in the paediatric population. A mucosal atomisation device (MAD) can be used for delivery of atomised particles of a drug to the nasal and oral mucosal surfaces. It is a latex free device that attaches directly to a leur-lock syringe and atomises medications, thus helps the drug reach a broader mucosal surface area, increasing its bioavailability. However, there have been no studies comparing sublingual atomised dexametomidine with oral midazolam (gold standard) for paediatric premedication in current literature. The primary aim of our study was to compare the sedation status between sublingual atomised dexametomidine and oral midazolam as premedication in children. Our secondary objectives were to assess the ease of child-parent separation, mask acceptance at induction and haemodynamic changes between the two groups.

METHODS

This was a prospective, double-blind, randomised control trial conducted in tertiary level hospital, after clearance from the Institutional Ethics Committee and appropriate clearance from the Clinical Trial Registry of India (CTRI / 201712 / 0190925, date of registration: 20 / 12 / 2017). It was carried out in children undergoing elective minor surgeries under general anaesthesia from December 2016 to March 2018.

Children with American Society of Anaesthesiologists Physical Status (ASA PS) 1 and 2, between ages 3 to 9 years, weighing 10 to 30 kg were included. Children with known allergy or hypersensitivity to dexametomidine/midazolam, parental/guardian refusal, severe developmental delay or behavioural problems, cardiac arrhythmia, or congenital heart disease, haemodynamic or respiratory instability, children at risk for airway obstruction (obstructive sleep apnoea or craniofacial syndrome), treatment with sedatives or anticonvulsants were excluded from the study. Children who spat, vomited, or refused sublingual or oral administration of medication were included in the study but excluded from analysis.

On the day prior to surgery, preoperative assessment was performed, and a written informed consent taken from parent/guardian. On the day of the surgery, the patients who met the inclusion criteria were randomly allocated into one of two groups: Group - D and Group - M. Randomisation was done using computer-generated random number sequence.

Patients in Group - D were given plain sublingual dexametomidine (100 µg/mL) 1.5 µg/kg body weight in a 1 cc syringe, with a mucosal atomisation device (MAD), 45 minutes before induction of anaesthesia. Patients in Group - M were given oral midazolam (5 mg/mL) 0.5 mg/kg body weight, mixed with strawberry-flavoured paracetamol syrup (120 mg/5mL) 15 mg/kg, 45 minutes before induction of anaesthesia. The child was shifted to the premedication area on a patient transport bed, along with the parent. A non-invasive blood pressure cuff (NIBP) and saturation probe were connected. Heart rate (HR), blood pressure (BP) and oxygen saturation (SpO2) were measured before administration of the test drug and every 15 minutes thereafter. A HR of less than 80 beats per minute or fall in heart rate of > 20 % from baseline and mean arterial blood pressure (MABP) of < 50 mmHg was considered significant. Sedation score was assessed at baseline and at every 15 minutes after administration of the drug, using modified observer assessment of alertness and sedation scale - MOAS/S. A sedation score of 3 or 4 was considered as satisfactory sedation. At the end of 45 minutes, the child was shifted to the operation room on the patient transport bed. The child-parent separation score was assessed, using a 3-point scoring system. A child-parent separation score of 1 or 2 was considered satisfactory. A NIBP cuff, saturation probe and electrocardiogram (ECG) electrodes were connected. Anaesthesia was induced on the patient transport bed using “steal induction” with graded increases in concentration of sevoflurane in oxygen, using a closed-circle system circuit. The acceptance of the mask by the child during induction was
assessed, using a 4-point scoring system. Mask acceptance was considered satisfactory if the score was 1 or 2.

Further anaesthetic management of the child, including choice of airway management, analgesia, and technique of extubation, was at the discretion of the anaesthesiologist attending the child. Vital parameters were recorded every 15 minutes during intraoperative period. At the end of the surgery, the child was awakened and behaviour at wake up was assessed, using a 4-point scoring system, and a score of 1 or 2 was considered satisfactory. The child was discharged from the recovery room after attaining a modified Aldrete score of more than 9. The scoring systems used for depth of sedation score, child-parent separation score, mask acceptance score and behaviour after wake up are illustrated in Table 1. A consort flow diagram is shown in Figure 1.

### Table 1. Scoring Systems - Modified Observer Assessment of Alertness and Sedation Scale (MOAA/S), Child - Parent Separation Score, Mask Acceptance Score and Wake - Up Behaviour / Behaviour at 30 Minutes

| Score | Observation |
|-------|-------------|
| 5     | Responds readily to name spoken in normal tone |
| 4     | Lethargic response to name spoken in normal tone |
| 3     | Responds only after name is called loudly and/or repeated |
| 2     | Responds only after mild prodding or shaking |
| 1     | Does not respond to mild prodding or shaking |
| 0     | Does not respond to deep stimulus |

| Score | Observation |
|-------|-------------|
| 3     | Patient fearful and crying, not quieted with reassurance |
| 2     | Patient slightly fearful and/or crying, quieted with reassurance |
| 1     | Patient unafraid, cooperative, or asleep |
| 1     | Calm and cooperative, or asleep |
| 2     | Fear of mask, easily calmed |
| 3     | Fear of mask, not easily calmed |
| 4     | Combative, angry |

| Score | Observation |
|-------|-------------|
| 1     | Calm and cooperative, or asleep |
| 2     | Not calm but could be easily calmed |
| 3     | Not easily calmed, moderately agitated or restless |
| 4     | Combative, excited, disoriented |

In our study, observer 1 was the postgraduate doctor who examined the child and enrolled according to the inclusion and exclusion criteria. The postgraduate doctor also monitored the child and recorded the sedation score preoperatively and every 15 minutes, child-parent separation score and mask acceptance score, and recorded any adverse events or rescue medication (glycopyrrrolate, atropine or adrenaline) until the patient went to the operation theatre. Observer 2 was the consultant anaesthesiologist who was responsible for randomisation, preparation of the drug accordingly, administration of the drug to the child, as well as documenting acceptability of the drug by the child.

Observer 3 was the postgraduate doctor posted with the paediatric patient who was responsible for the intraoperative haemodynamic monitoring, assessment of wake-up score and any adverse events intraoperatively, along with the rescue medication administered. Observer 4 was the nursing staff in charge in the recovery room who monitored the child postoperatively, scored the child’s behaviour in the recovery room at the end of 30 minutes and discharged the child from recovery room.

Our sample size was calculated based on pilot study data. We used a confidence level (1 - α) of 95 %, and power of the study (1 - β) of 90 %. We took a clinically significant difference of 30 % for sedation status at 45 minutes between the two groups. A calculated sample size of 27 patients was required in each group. To allow for dropouts, 30 patients were enrolled in each group.

**Statistical Analysis**

The results were analysed using the Statistical Package for the Social Sciences (SPSS) V17 statistical package (IBM Corporation, United States). Qualitative data were analysed using chi-square test. Quantitative data were analysed using student’s t-test. Intra-group analysis of haemodynamics (HR and MABP) and sedation levels was done using repeated measures ANOVA (Analysis of Variance). A P - value of < 0.05 was considered statistically significant.

**RESULTS**

Both groups were comparable in terms of gender, height, and weight. There was a statistically significant, although not clinically significant, difference between Group D and M, in terms of age, with P - value of 0.03.

Both groups were also comparable in terms of types and duration of surgeries, with P - value 0.1297 and 0.9630, respectively. There was no significant difference in acceptability of the drugs in either group with a P - value of 0.3719.

Children in Group - D had significantly deeper levels of sedation (Sedation score 2 and 3) than those in Group - M (Sedation score 3 or 4), with P - value < 0.0001 (Figure 2).

However, for the purpose of this study, a sedation score of 3...
or 4 was considered as satisfactory sedation. The maximum sedation in the children in Group - D was at 30 and 45 minutes.

| Demographic data     | Group - D | Group - M | P - Value |
|----------------------|-----------|-----------|-----------|
| Age in years (Mean ± SD) | 5.23 ± 1.97 | 4.3 ± 1.24 | 0.0317    |
| Gender (Male / Female) | 27 / 3    | 26 / 4    | 0.6876    |
| Height in centimeters (Mean ± SD) | 107.23 ± 14.1 | 103 ± 8.14 | 0.1606    |
| Weight in kilogram (Mean ± SD) | 16.74 ± 5.13 | 15.44 ± 3.76 | 0.2675    |
| Types of surgeries   |           |           |           |
| Herniotomy           | 10        | 6         | 0.1297    |
| Orchidopexy          | 1         | 6         |           |
| Circumcision         | 3         | 5         |           |
| Urological           | 6         | 2         |           |
| Others               | 10        | 11        |           |
| Duration of surgery  | Duration of surgery (minutes) (Mean ± SD) | 64.83 ± 46.08 | 64.33 ± 36.38 | 0.9630 |

Table 2. Demographic Data, Types of Surgeries and Duration of Surgeries

*Group - D = Group dexmedetomidine
† Group - M = Group midazolam
‡ SD = Standard deviation

Children in Group - M were more uniformly sedated at each time points, and there were no children with undesirably deep sedation (sedation score of 1 or 2). Both groups had acceptable scores for child-parent separation of 1 or 2, and the child-parent separation score was comparable between the two groups, with P - value 0.895. Mask acceptance was assessed during inhalational steal induction of the child. The mask acceptance at induction was significantly better in Group - M, than Group - D, with a P - value of 0.007 (Figure 3).

Haemodynamics were assessed at baseline and at every 15 minutes till induction of anaesthesia (Figure 4). There was a significant decrease in the HR in Group - D as compared to Group - M at 30 minutes and 45 minutes with P - value of 0.003 and < 0.0001, respectively. However, none of the children had any clinically significant fall in heart rate that required intervention. There was no significant decrease in MABP in both Group - D and Group - M from baseline. MABP is comparable at 15, 30 and 45 minutes, in both groups, with P - value of 0.9161, 0.5348 and 0.1731 respectively, and is not statistically significant.

Using repeated measures ANOVA, the HR and MABP changes within Group - D and M were also analysed. In Group - D, there was significant haemodynamic variation, with maximum fall in heart rate at 30 and 45 minutes, compared to baseline HR and HR at 15 minutes. However, the change in HR was not significant between 30 and 45 minutes. There was also a significant decrease in MABP at the end of 45 minutes in Group - D. Nevertheless, there was no drop at 30 minutes, indicating that significant MABP changes occur after at least 30 minutes of administration of sublingual dexmedetomidine. In Group - M, there was no statistically significant variation in the HR or MABP at any time point.

The behaviour of the child at wake up and behaviour at 30 minutes were comparable (P - value 0.194 and 0.299, respectively). Time till discharge from recovery room was also assessed (P - value 0.96) and found to be statistically insignificant.

**DISCUSSION**

Pre-operative anxiety is commonly seen in children coming for surgery with an incidence of at least 60%. Premedication is required to alleviate anxiety and fear, allowing smooth separation from parents, and allow easy acceptance of needle prick for intravenous cannulation and anaesthesia induction. Extreme anxiety and stress before surgery has also been reported to result in negative post-operative sequelae such as emergence delirium, maladaptive behaviour and increased post-operative pain.1,2 Hence, relieving preoperative anxiety is an important concern for the paediatric anaesthesiologist.

There are various methods to decrease preoperative anxiety, including pharmacologic and non-pharmacologic methods. The ideal premedication in children should be acceptable, have atraumatic route of administration, rapid and reliable onset, with minimal side effects and rapid elimination. Midazolam is commonly for premedication in children as it provides effective sedation, anxiolysis, anti-emetic and varying degrees of anterograde amnesia. Oral midazolam is often considered the gold standard paediatric sedative.
Premedication. However, it has certain undesirable effects such as impaired cognitive function, paradoxical reactions, long-term behavioural changes, and respiratory depression.

Dexmedetomidine demonstrates few unique and unmatched properties. It possesses sedative and analgesic qualities, while maintaining upper airway tone. It also decreases the emergence agitation after sevoflurane-based anaesthesia in children. Additionally, it is a tasteless and odourless drug, making it a near ideal sedative. Various studies have been done that prove that dexmedetomidine is a safe and effective drug for paediatric procedural sedation, such as magnetic resonance imaging (MRI), computed tomography (CT) scans and transthoracic echocardiography, as well as for preoperative sedation.

Oral and sublingual premedication are both painless methods of premedication. Although bioavailability of oral midazolam is poor (15 - 35 %), a study done by Chhibber et al. found that oral midazolam in a dose of 0.5 mg/kg (five times the intravenous dose) was the most effective with the least side effects. Oral midazolam has a bitter taste and is highly unpalatable. It is made more palatable by mixing it with honey, dextrose, or flavoured paracetamol syrup. In our study, we chose to mix midazolam with strawberry-flavoured paracetamol syrup for improved oral acceptance. Dexmedetomidine is a tasteless drug, and hence was not mixed with additional agents for palatability. Dexmedetomidine also has a poor oral bioavailability (~16 %) but has a transmucosal bioavailability of 82 %. A study done by Pant et al. showed that dexmedetomidine 1.5 µg/kg sublingually 45 minutes prior to surgery produced safe and adequate sedation in children. In our study, sublingual dexmedetomidine was used in a dose of 1.5 µg/kg as well. We further augmented the bioavailability by using a mucosal atomization device that aids in better dispersion of the atomised drug, as well as decreases the volume of the drug that could potentially travel to the oropharynx.

We included a total of sixty patients in our study. Thirty of the patients were given sublingual dexmedetomidine 1.5 µg/kg using a MAD and thirty of them were given 0.5 mg/kg of oral midazolam, mixed with strawberry-flavoured paracetamol syrup 15 mg/kg. Both drugs were given 45 minutes prior to induction of anaesthesia.

In our study, we found that the children who were premedicated with dexmedetomidine prior to surgery were significantly more deeply sedated than those premedicated with oral midazolam, with a P-value of < 0.0001. This corresponds to studies done by Yuen et al. and Ghali et al. while comparing intranasal dexmedetomidine and midazolam. However, such intense and deep levels of sedation, as seen here with sublingual atomised dexmedetomidine, might not be required for routine paediatric anxiolysis and premedication, and the light sedation that was achieved by oral midazolam was more desirable. In addition, onset of sedation in the two groups was also analysed. We found that the maximum sedation in Group - D was between 30 and 45 minutes, whereas Group - M had a more uniform distribution of light sedation starting from 15 minutes after drug administration, with sedation gradually wearing off after 30 minutes.

We found that both groups had comparable and acceptable child-parent separation scores, with a P-value of 0.895. The reason for acceptable children - parent separation in Group - D was likely to be the deeper levels of sedation. The children in Group - M, although less sedated, had acceptable child-parent separation scores as well and we attribute this to the anxiolytic property of midazolam. On the contrary, Pant et al. found that sublingual dexmedetomidine produces better child-parent separation than sublingual midazolam.

Children who were administered oral midazolam, although less sedated than those in the dexmedetomidine group, had better levels of mask acceptance at induction (P = 0.007). The children in Group - D, although more deeply sedated preoperatively than those in Group - M, were found to be more easily arousable during anaesthetic gas steal induction and were found to be less consolable upon arousal. The children in Group - M, although less sedated were also less anxious and readily accepted the mask during induction. This finding could also be accredited to the potent anxiolytic property possessed by midazolam. This finding was consistent with studies done by Pant et al. and Akin et al. However, Sheta et al. suggest that intranasal midazolam produces poorer mask acceptance than intranasal dexmedetomidine.

When compared to the children in Group - M, those in Group - D had a statistically significant decrease in the heart rate at 30 and 45 minutes. However, this fall in heart rate was not clinically significant and none of the children had a drop in HR that required any pharmacological intervention. This supports evidence from previous studies by Pant et al. Yuen et al. and Kumar et al. Within Group - D, the maximum fall in HR and MABP was between 30 and 45 minutes, correlating with the time-period of maximum sedation in this group as well. In Group - M, there was no significant fall in HR or MABP at any time point, supporting the existing evidence that midazolam does not cause cardiovascular depression.

Although behaviour at wake up, behaviour at 30 minutes and time till discharge from recovery room was comparable between the two groups with a P-value of > 0.05, there are multiple confounding factors in play, as the type of surgeries, analgesia used, and airway instrumentation (i.e., mask holding, laryngeal mask airway or endotracheal tube) used were not standardised, and thus, might not be reflective of either drug. This is one of the limitations of this study. Including surgeries with similar profile, standardizing the analgesia and airway management, and documentation of analgesic requirements in the postoperative period, can help for better understanding of these drugs for paediatric premedication.

Conclusions

Atomised sublingual dexmedetomidine when compared to oral midazolam as a premedicant in children undergoing elective minor surgery produced significantly greater sedation, with low-normal heart rate. Both groups had acceptable and comparable child-parent separation. However, mask acceptance was significantly superior with oral midazolam. We accredit the comparable child-parent separation and superior mask acceptance, although less sedated, in the midazolam group, to its anxiolytic property. We conclude that sublingual atomised dexmedetomidine, in a
dose of 1.5 µg/kg is not a suitable alternative to oral midazolam 0.5 mg/kg for paediatric premedication.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

Disclosure
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