Oral transmucosal midazolam premedication for preschool children

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Purpose: To evaluate the acceptance and effectiveness of 0.2 $mg \cdot kg^{-1}$ of oral transmucosal midazolam as a premedicant in infants and preschool children.

Method: In a randomized, prospective double-blind placebo controlled study, 44 healthy children, between the ages of eight months to six years, presenting for elective surgery were divided in two groups. The medicated group received 0.2 $mg \cdot kg^{-1}$ of injectable midazolam mixed with an equal volume of strawberry syrup and the placebo group received plain syrup 0.08 $ml \cdot kg^{-1}$. Medications were placed on the anterosuperior aspect of the child's tongue in 3-5 aliquots of 0.2-0.4 ml. A blinded observer assessed the acceptance of the medication by willingness to open the mouth for the next aliquot and the efficacy of the medication was assessed by ease of separation from the parent.

Results: Ninety-six percent of the children in the placebo group and 95% in the midazolam group willingly accepted the medication. Separation of children from parents was successful in 95% of the medicated children compared with 59% in the placebo group ($P = 0.006$).

Conclusion: Oral midazolam in thick strawberry syrup, administered in small aliquots via the oral transmucosal route was well accepted and proved to be an effective premedicant in infants and preschool children.

Objectif : Évaluer l'acceptation et l'efficacité de 0,2 $mg \cdot kg^{-1}$ de midazolam transmuqueux administré par voie orale comme prémédication chez des bébés et de jeunes enfants.

Méthode : Ont participé à l'étude randomisée, prospective et en double aveugle contre placebo, 44 enfants en santé, de huit mois à six ans, répartis en deux groupes et qui devaient subir une intervention chirurgicale planifiée. Le groupe à l'étude a reçu 0,2 $mg \cdot kg^{-1}$ de midazolam injectable dans un volume égal de sirop de fraise. Le groupe placebo a reçu seulement 0,08 $ml \cdot kg^{-1}$ de sirop. Le médicament a été déposé sur la face antérosupérieure de la langue de l'enfant en 3-5 parties égales de 0,2-0,4 ml. Un observateur impartial a évalué l'acceptation du médicament par la bonne volonté à ouvrir la bouche pour recevoir une autre dose. L'efficacité a été mesurée par la facilité de l'enfant à se séparer de ses parents.

Résultats : Le médicament a été facilement accepté par 96 % des enfants du groupe placebo et 95 % du groupe midazolam. La séparation des enfants d'avec leurs parents s'est bien passée chez 95 % des enfants médicamentés et chez 59 % des enfants du groupe placebo ($P = 0{,}006$).

Conclusion : Le midazolam administré par voie orale et en petites doses égales dans un sirop de fraise a été bien accepté et a été efficace chez des bébés et de jeunes enfants.

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BEFORE the induction of general anesthesia, infants and preschool children frequently need medication to decrease their anxiety and to facilitate their separation from parents. Midazolam is the most commonly used premedicant for this purpose.[1] In 1998, Kain *et al.* reported that premedication with midazolam was more effective in reducing anxiety in preschool children than was parental presence at induction of anesthesia.[2] The same investigators more recently reported that midazolam premedication before anesthesia reduced negative behaviour for the first week following surgery.[3] Although premedicating with midazolam has clear advantages, there are drawbacks with oral, sublingual, or intranasal administration of the medication to children.[4–10]

The disadvantages of oral administration are that a relatively large dose (0.5-1.0 $mg \cdot kg^{-1}$) of midazolam is required because of first-pass metabolism in the portal circulation yet the peak effect is seen in about 30 min[4,11] and children dislike its bitter taste. Furthermore, as Viitanen *et al.* recently reported, oral midazolam in a dose this large may delay recovery after brief sevoflurane anesthesia.[12] As an option to orogastric administration, midazolam can be directly delivered into the child's systemic circulation via the nasal, sublingual, and oral transmucosal routes. This avoids the first pass metabolism in the liver and allows for a 40-50% higher serum concentration of the medication.[13,14] Thus, a smaller dose of the medication is required. Intranasal administration of midazolam is easily accomplished, but is poorly tolerated by children due to the irritation and stinging of the nasal mucosa.[7] Administering midazolam sublingually has had some success,[7,9,15] however the medication must be held under the tongue for at least 30 sec using this method. This requires cooperation that is difficult to achieve in infants and preschoolers and the medication is often rejected because of its bitter taste.[7]

We hypothesized that we could achieve the advantages of intranasal or sublingual administration (i.e., short onset time and small dose) without the associated disadvantages (i.e., mucosal irritation and bitter taste) by adding midazolam to thick sweet syrup and administering it via small aliquots in the mouth. This would prolong the contact and absorption of the midazolam from the oral mucosa before the syrup reached the pharynx to be swallowed. We conducted a randomized double-blind placebo controlled study that compared the effect of oral transmucosal delivery of midazolam in flavoured syrup to placebo. We evaluated the acceptance of the medication and ease of separation of children from their parents before induction of general anaesthesia. The dose of 0.2 $mg \cdot kg^{-1}$ midazolam selected for this study was similar to the dose found to be effective intranasally.[5–8]

Methods

Following approval from our Institutional Review Board and obtaining parental written informed consent, we studied forty-four healthy children between the ages of eight months and six years presenting for elective surgery. The study did not include subjects with hepatic, renal and gastrointestinal dysfunction, anticipated difficult airway, or inpatients with existing *iv* access. Study patients were randomly assigned to one of the two groups, midazolam or placebo. The placebo group received 0.08 $ml \cdot kg^{-1}$ strawberry flavoured syrup (Gordon Food Service, Grand Rapids, MI) and diluted with simple syrup (HUMCO, Texarakana, TX) by our pharmacy. The midazolam group received injectable midazolam (5 $mg \cdot ml^{-1}$) 0.2 $mg \cdot kg^{-1}$ in an equal volume of the strawberry syrup. Approximately 15 min before induction of anesthesia, a nurse administered the assigned medication in 0.2-0.4 ml aliquots on the antero-superior aspect of the tongue.

A blinded observer (same observer for all patients) scored the patient's behaviour during the preoperative period using the scales presented in Table I. Apprehension and sedation scores were assigned at the time of drug administration and at five min intervals until the induction of anesthesia. Palatability of midazolam was graded as good acceptance when the children opened the mouth for accepting subsequent aliquots of the medication or poor acceptance when force was required to open mouth after the initial aliquot. Anesthesia care-giver assigned to the case separated the child from parents and the blinded observer assigned a separation score (Table I). Separation was considered successful if the child separated happily or without crying (1&2) and considered unsuccessful if the child separated with crying, or with restraint (3&4). Parents were allowed to be present for induction of anesthesia only if the child failed to separate.

Anesthesia was induced with inhalation of either halothane or sevoflurane in an oxygen / nitrous oxide mixture (30 / 70%). The blinded observer recorded acceptance of the mask and quality of induction, the lowest SpO_2 and any untoward incidents. Maintenance of anesthesia was left to the discretion of the attending anesthesiologist assigned to the case. Postoperatively, the times to spontaneous eye opening, first response to verbal command, and PACU discharge were noted. Additionally, the PACU nurse assigned a behaviour score every five minutes for 30 min after awakening. At the time of discharge from

TABLE I Preoperative Behaviour Scales

Acceptance Score (palatability)		
Good	1	Readily accepts
	2	Dislikes, but accepts
Poor	3	Held down / forced to accept
	4	Refuses to open mouth *after tasting*
Apprehension Score (anxiety)		
1		None
2		Little / minimal expression of fear
3		Moderate / expresses fear / apprehension
4		Excessive / vocal display of fear / apprehension
Sedation Score		
1		Asleep / not readily arousable
2		Asleep / responds slowly to gentle stimulation
3		Drowsy / readily responds
4		Awake / calm & quiet
5		Awake / active
Separation Score		
Successful	1	Excellent: happily separated
	2	Good: separated without crying
Unsuccessful	3	Fair: separated with crying
	4	Poor: need for restraint
Cooperation Score at Induction		
1		Cooperative
2		Mildly resistant
3		Resistant to placement of mask to face

TABLE II Demographic and Other Variables Measured (mean ± SD)

	Placebo (n=22)	*Midazolam (n=20)*	*P*
Age (yr)	4.0 ± 1.7	3.5 ± 2.0	0.481
Weight (kg)	17.7 ± 5.3	15.9 ± 5.3	0.284
Preoperative anxiety	1.4 ± .7	1.3 ± .4	0.407
Separation time (min)	15.2 ± 8	16.1 ± 6	0.689
Anesthesia time (min)	67 ± 35	81 ± 47	0.304
Eye opening (min)	29 ± 27	24 ± 16	0.511
PACU stay (min)	93 ± 43	105 ± 57	0.441
Parental satisfaction	7.3 ± 3.2	9.1 ± 1.1	0.049*

*$P < .05$

TABLE III Acceptability and Efficacy

	Placebo (n=22)	*Midazolam (n-20)*	*P*
Drug acceptance	21 (96 %)	19 (95%)	0.945
Successful separation	13 (59 %)	19 (95%)	0.006*
Parental presence	6(27%)	1 (05%)	0.053

*$P < .01$

the PACU, the parents were asked to rate their satisfaction with the premedication on a visual analogue scale from 0 to 10 (ie., 0= extremely dissatisfied; 10= extremely satisfied).

Power analysis demonstrated that 21 children per group would be required to detect a difference in separation scores between groups (i.e., midazolam 15% *vs* placebo 50% poor separation; α=0.05; ß=0.2). Thus the study has a power of >0.8 to detect a 35% difference in separation. Chi-square with Fisher's exact tests was used to analyze non-parametric data (i.e., behavioural scores such as apprehension, separation). Paired and unpaired t tests were used to analyze continuous data (e.g., time to awaken, time to discharge) where applicable. A P value < 0.05 was considered statistically significant.

Results

Forty-four children were studied, 20 received midazolam and 22 placebo. In two children who refused premedication before tasting, we were unable to evaluate the palatability or efficacy. They were excluded from further analysis thereby explaining the unequal size of the two groups. There were no differences in the demographic variables between the two groups (Table II). Pre-drug apprehension scores were similar between the two groups. Apprehension scores were not different at any time (5, 10 and 15 min.) after drug administration between the two groups. Predrug sedation scores at 5, 10 & 15 min after the administration of medication were not different in the two groups.

Nineteen children in the midazolam group willingly accepted the medication (i.e., spontaneously opened the mouth to accept more medication), although seven verbally or by facial grimacing indicated that they did not like the taste. Twenty-one children of the 22 in the placebo group also accepted the medication willingly. One child in each group required restraint to accept medication after tasting.

The mean time from drug administration to attempted separation from the parents was similar in the two groups (Table II). Midazolam facilitated successful separation from parents in 19 / 20 (95%) children compared with 13 of 22 (59%) receiving placebo, $P = 0.006$. Although nine of 22 children in the placebo group cried or failed to separate, only six parents were asked to accompany their child to the operating room (three children separated with crying). Nineteen of 20 children who received midazolam were successfully separated from parents; only one required parental presence at induction of anesthesia (P = NS). Thirteen children in the placebo group and eight in the midazolam group resisted or refused to accept the mask (P = NS).

Adverse events included one episode of laryngospasm at induction of anesthesia in each group. Both occurred at the time of attempted intubation. One child required positive pressure ventilation and the other required succinylcholine before a second

attempt at intubation. Both the episodes were most likely due to inadequate depth of anesthesia. Postoperatively the two groups were similar in time to eye opening, incidence of agitation and time to discharge from PACU (Table II).

Discussion

This study demonstrates that oral transmucosal midazolam (0.2 $mg \cdot kg^{-1}$) given in small aliquots over the antero-superior aspect of the tongue in preschool children is an effective premedicant. The most important criterion of a satisfactory premedicant for preschool children is its ability to facilitate separation of the child from parents. In this study, a small dose of midazolam via the oral transmucosal route appeared to have achieved the desired effect. Although disliked by some children, the overall acceptance of midazolam in fruit syrup was similar to placebo (fruit syrup). This technique is an improvement over intranasal administration of midazolam which children intensely disliked.[7] It may also have some advantage over sublingual administration of midazolam, because of its bitter taste and the potential difficulty for preschool children to comply with the instructions.

Oral midazolam in a dose of 0.5-1.0 $mg \cdot kg^{-1}$ diluted in a sweetened liquid is the most common premedicant in preschool children.[3] We considered but decided not to include a group of oral midazolam in our study to compare with oral transmucosal midazolam, because true blinding would have been a problem. It would appear both oral and oral transmucosal routes of administration of midazolam are effective premedicants in infants and preschool children. The latter route may offer a benefit in terms of cost savings. Considering the example of a 12 kg child, a single dose of 0.5 $mg \cdot kg^{-1}$ oral midazolam suspension (Roche laboratories, this was not available at the time of our study) would cost $9.13 compared with $3.55 for 0.2 $mg \cdot kg^{-1}$ of same preparation via the oral transmucosal route. Furthermore, the peak effect of oral transmucosal midazolam of 10 min compares favourably with 30 min after an oral dose.[11] A recent study showed that an oral dose of 0.5 $mg \cdot kg^{-1}$ midazolam given before short surgical procedure (adenoidectomy) delays awakening compared with placebo.[12] Our data indicated that a smaller dose of 0.2 $mg \cdot kg^{-1}$ midazolam given by the oral transmucosal route is an effective premedicant and produces rapid onset of action. We found no evidence of delayed recovery in those receiving the smaller (0.2 $mg \cdot kg^{-1}$) dose of midazolam, however, in our study, we did not control the type of surgery and the average duration of anesthesia was longer.

Karl *et al.* showed that children prefer the sublingual route of administration of midazolam to the intranasal route.[7] Although infants and preschool children require premedication more often than other age groups, in their study only 20% of infants and 44% of preschool children complied with the instructions of sublingual administration. Khalil *et al.* showed compliance in 67% of the preschool children with sublingual route.[15] In the present study we achieved a compliance rate of 95% in infants and preschool children, which is higher than previously demonstrated with sublingual administration of midazolam.

Sedation scores were not different at any time after drug administration between the two groups. This was perhaps because children were encouraged by parents to play with toys in the preoperative holding area under the supervision of a nurse. These fascinating new toys distracted all the children and distracted children showed no apprehension and all of them maintained a sedation score of 4-5 in both the groups after receiving either premedicant.

In the present study, 95% of children separated well from parents. This is better than the 75% to 80% achieved with sublingual administration of the same dose of midazolam.[7] Although children separated well from parents, some of the children resisted the application of facemask for induction of anesthesia. Other investigators[7,11] had similar experiences. Khalil *et al.* recommended a higher dose of sublingual midazolam to induce deep sedation before application of mask to the face.[15] We felt that deep sedation would be unsafe in our busy pediatric surgery setting where one nurse watches up to five to six children at one time.

This study was designed primarily to evaluate the efficacy of the premedicant in the preoperative period. Recovery characteristics were not the primary focus of the study. That is why we did not control the type and duration of surgery and of anesthesia. Further studies will be required to determine the recovery profile of this dose after short surgical procedures. The scoring scales used for palatability, apprehension, sedation, separation and co-operation were somewhat arbitrary, however, one blinded observer assigned all the scores so the variability of observations was minimal.

In conclusion, this study shows that the delivery of a small aliquot of injectable midazolam mixed with thick strawberry syrup placed on the anterosuperior aspect of the tongue is an effective, simple and economical route to deliver premedication to infants and preschool children. This mode of delivery was willingly accepted and resulted in successful separation from parents in 95% of children.

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