Evidence-based clinical update: Does premedication with oral midazolam lead to improved behavioural outcomes in children?

[Mise à jour basée sur des données probantes : Améliore-t-on le comportement des enfants par une prémédication au midazolam par la bouche ?]

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Purpose: The purpose of this evidence-based clinical update was to identify the best evidence to determine if behavioural outcomes are improved in children after oral midazolam premedication.

Methods: A literature search was conducted using both PubMed and OVID programs, utilizing the terms "midazolam", and either "premedication" or "preoperative treatment". Search limits that were employed included randomized controlled trials (RCTs), English language, human studies, children aged 0–18 yr, and publication dates 1990 – present (January 2006). A review of the 171 abstracts obtained was undertaken and, of these, 30 papers were identified that concerned oral midazolam in children prior to general anesthesia, and that involved a RCT with a placebo or control arm. These studies were assigned levels of evidence, and grades of recommendation were made according to Centre for Evidence-Based Medicine criteria.

Results: Oral midazolam premedication in children was found to reduce the anxiety associated with separation from parents/guardians, and with induction of anesthesia. Recovery times are not significantly delayed. There is no consistent evidence to suggest a reduction in the phenomenon of emergence agitation. Evidence suggesting an improvement in behavioural outcomes at home is also inconsistent.

Conclusion: Premedication with midazolam 0.5 $mg \cdot kg^{-1}$ *po* administered 20–30 min preoperatively, is effective in reducing both separation and induction anxiety in children (grade A recommendation), with minimal effect on recovery times. However improved postoperative behavioural outcomes in the postanesthesia care unit, or at home cannot be predicted on a consistent basis.

***Objectif** : L'objectif de cette mise à jour basée sur des données probantes est d'évaluer les meilleures données sur l'amélioration du comportement des enfants après une prémédication au midazolam.*

***Méthodes** : Une recherche d'articles a été effectuée avec les programmes PubMed et OVID, en utilisant les termes « midazolam », ainsi que « premedication » ou « preoperative treatment ». On a limité la recherche aux études contrôlées randomisées, en langue anglaise, sur des êtres humains, sur des sujets de 0 à 18 ans, publiées de 1990 à maintenant (janvier 2006). Après examen des 171 résumés obtenus, on a retenu 30 articles qui portaient sur le midazolam par voie orale chez les enfants avant une anesthésie générale et qui comportaient une randomisation avec un groupe placebo ou témoin. Les études ont été évaluées selon le niveau de preuve et on leur a donné une cote selon le barème du « Centre for Evidence-Based Medicine ».*

***Résultats** : On a trouvé que midazolam par voie orale diminuait l'anxiété survenant à la séparation des parents ou tuteurs et à l'induction de l'anesthésie. Les temps de récupération n'étaient pas prolongés significativement. Il n'y a pas de données solides qui suggéreraient une diminution du phénomène d'agitation à l'émergence. De même, les données sur l'amélioration du comportement au retour à la maison sont contradictoires.*

***Conclusion** : Une prémédication avec du midazolam 0,5 $mg \cdot kg^{-1}$ administré par voie orale 20–30 min avant la chirurgie est efficace pour diminuer l'anxiété liée à la séparation et à l'induction (recommandation de niveau A), avec peu d'effets sur le temps de récupération. Toutefois, on ne peut pas prédire avec certitude les comportements à la salle de réveil ou au retour à la maison.*

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Accepted for publication August 31, 2006.

Revision accepted September 18, 2006.

OVER the years, various types of premedication have been administered to children prior to the induction of anesthesia. With the advent of volatile agents that lack pungency and airway irritability, the need for a routine antisialogogue premedicant has waned. The main goal of premedication currently is to allay anxiety during the various phases of the perioperative period. Midazolam, a relatively short-acting benzodiazepine, has found favour in this regard, and is most commonly given by the oral route in children. A considerable body of evidence about this form of premedication has now accumulated, and this evidence-based clinical update (EBCU) will evaluate the benefit of this intervention, particularly with respect to behavioural outcomes.

Clinical question

The clinical question for analysis was as follows: *Does premedication with oral midazolam lead to improved behavioural outcomes in children?* Specifically, this update seeks to determine whether clinical outcomes are improved at separation from parents/guardians, at induction, in the postanesthesia care unit (PACU), and once the child has returned home.

Methods

A structured literature search was conducted in accordance with the EBCU format of the *Journal* (posted at: www.cja-jca.org). Search methodology entailed the use of both PubMed and OVID programs, utilizing the terms "midazolam", and either "premedication" or "preoperative treatment". Search limits that were employed included randomized controlled trials (RCTs), English language, human studies, children aged 0–18 yr, and publication dates 1990 – present (January 2006). We had previously determined that there were no systematic reviews of RCTs on this topic in the literature using these search terms. This methodology produced almost identical results using the two search platforms. One hundred and seventy-one abstracts were obtained, which were then reviewed by two of the authors (R.G.C. and U.N.). If it was clear that the study did not address premedication prior to general anesthesia, did not contain a placebo or control group, did not entail midazolam being given by the oral route, or was not a RCT, then that study was withdrawn from the data base. If there was any doubt as to the nature of the study, the full version of the paper was obtained.

Following this initial screening, 30 papers remained for further analysis.[1–30] A hand search of the bibliographies of these 30 papers did not identify any further key studies. Complete versions of papers were then reviewed in detail by all four authors. An Excel spreadsheet was constructed, to collect key data and facilitate the grading of the studies. Three of the authors (R.G.C., A.E., M.J.C.), all experienced pediatric anesthesiologists, graded the papers as being either good quality (level 1b) or poor quality (level 2b) RCTs, and assigned each study a level of evidence according to the criteria of the Oxford Centre for Evidence-Based Medicine.[31] With three independent anesthesiologists evaluating, a simple majority of opinion determined the grading. The criteria used to determine the quality of individual RCTs included, but were not limited to, the confidence intervals, power analysis/sample size calculation, standardization of anesthesia and surgery, validation of the anxiety scoring system and standardization of other factors, such as parental presence at induction. Detailed review of the 30 papers allowed the authors to answer in whole or in part the clinical questions posed. Grades of recommendation were assigned to the evidence, as defined by the Centre for Evidence-Based Medicine (Appendix), together with levels of evidence criteria for individual studies.

Review of current best evidence

General quality of papers reviewed

The 30 papers reviewed varied considerably in scientific quality. All studies fell under the category of RCTs, however the methodology was very variable. The majority were designed to compare oral midazolam with placebo or control, however some studies compared these two with other drugs or interventions, such as parental presence at induction, or music therapy. Some studies were aimed at answering another primary question, but so long as data was provided that could answer any of the clinical questions posed in this review, these studies were included.

Table I provides a summary of the key methodological components of the studies reviewed. Of the 30 papers, 14 included a detailed sample size calculation, and only 11 included details of the randomization methodology. Twenty studies were double-blinded, nine were single-blinded, and one was not blinded. Anesthesia induction drugs were standardized in 24 studies; the remaining six were either unspecified or allowed for variation. Techniques for anesthesia maintenance were standardized in 17 studies; the remaining 13 had an unspecified anesthetic technique, or allowed for variation. Surgical procedures were multiple in nature in 20 studies; in ten studies the procedures were specified (e.g., only adenoidectomy, or only inguinal hernia repair). All studies provided details of the statistical analysis, the most frequent

TABLE I Summary of study characteristics

Ref	*Induction*	*Maintenance*	*Surgery*	*Midazolam (mg·kg^{-1})*	*Sample size calculation*	*Blinding*	*Anxiety score*	*Parents present*
1	Standard inhalation	Unspecified	Variable	0.25/0.5/0.75	No	Double	4 point	Separated
2	Standard inhalation	Standard	Hernia	0.45	No	Single	4 point	Unspecified
3	Variable	Variable	Variable	0.25/0.5	No	Double	4 point	Variable
4	Standard inhalation	Standard	Variable	0.5	No	Double	4 point	Separated
5	Standard inhalation	Standard	Variable	0.5/0.75/1.0	Yes	Double	4 point	Separated
6	Standard inhalation	Standard	Hernia	0.45	No	Single	N/A	Unspecified
7	Variable	Variable	Unspecified	0.6	No	Double	4 point	Separated
8	Variable	Standard	Unspecified	0.5	No	Double	4 point	Present
9	Standard inhalation	Standard	Variable	0.5	Yes	Single	4 point	Present
10	Standard inhalation	Unspecified	Unspecified	0.5	Yes	Double	OSBD-R	Present
11	Standard *iv*	Variable	Variable	0.75	No	Double	3/4 point	Present
12	Variable	Unspecified	Variable	0.2	No	Double	4 point	Separated
13	Variable	Standard	Tonsil/Aden	0.5	No	Double	4 point	Present
14	Standard *iv*	Standard	Abdo/GU	0.75	No	Double	4 point	Separated
15	Standard *iv*	Standard	Variable	0.5	No	Double	4 point	Separated
16	Unspecified	Unspecified	Unspecified	0.5	No	Partial	3 point	Variable
17	Standard inhalation	Unspecified	Variable	0.5	Yes	Single	mYPAS, ICC	Separated
18	Standard inhalation	Standard	Variable	0.25/0.5/0.75	Yes	Double	3/4 point	Separated
19	Standard inhalation	Standard	Variable	0.5	Yes	Double	mYPAS	Separated
20	Standard *iv*	Standard	Adenoids	0.5	Yes	Double	N/A	Unspecified
21	Standard inhalation	Standard	Myringotomy	0.5	No	Single	N/A	Unspecified
22	Standard *iv*	Standard	Adenoids	0.5	Yes	Double	N/A	Unspecified
23	Standard inhalation	Variable	Variable	0.5	Yes	Single	mYPAS	Unspecified
24	Standard inhalation	Unspecified	Variable	0.2	Yes	Double	3 point	Variable
25	Standard inhalation	Standard	Variable	0.2	Yes	Single	N/A	Separated
26	Standard inhalation	Standard	Variable	20 mg fixed	No	Double	OAA/S	Unspecified
27	Standard inhalation	Unspecified	Variable	0.5	Yes	Unblinded	mYPAS	Present
28	Standard inhalation	Unspecified	Variable	0.5	Yes	Single	mYPAS	Separated
29	Standard inhalation	Standard	Abdominal	0.1/0.25/0.5	Yes	Double	mYPAS	Separated
30	Standard inhalation	Standard	Myringotomy	0.5	Yes	Double	mYPAS	Separated

mYPAS = Modified Yale Preoperative Anxiety Score; OAA/S = Observer's Assessment of Alertness/Sedation score; ICC = induction compliance checklist; OSBD-R = revised observational scale of behavioural distress.

instruments being ANOVA, χ^2, and *t* test, depending on the variables being analyzed. In 20 studies the design specified whether parents were present or not for induction; in the remaining ten, this was unspecified or variable. The majority of papers used a simple three- or four-point scale to grade anxiety, without evidence as to scale validation, rather than employing a more robust, validated scoring system such as the Modified Yale Preoperative Anxiety Score (mYPAS). The mYPAS is the current gold standard for evaluating anxiety at induction of anesthesia in children.

Other variables included the age range studied; with the exception of one study,[26] however, all children studied were under 12 yr of age. Doses of midazolam ranged from 0.1 mg·kg^{-1} to 1 mg·kg^{-1}, the most common dose being 0.5 mg·kg^{-1}. Two studies modified the oral route, allowing the drug to be absorbed sublingually[18] or transmucosally[24] before being swallowed. Five studies included midazolam at different doses. The mean sample size was 32 subjects (range 12–54) for the midazolam groups and 30 subjects (range 12–52) for the placebo or control groups.

Following detailed evaluation of the scientific methodology, the authors determined that 14 of the studies were high quality RCTs. Table II summarizes the main outcomes of all 30 papers.

Separation anxiety

Anxiety at separation from the parent or guardian was evaluated in 14 studies. Of these, eight showed a reduction in separation anxiety with midazolam, and the remaining six did not show a statistically significant benefit. When considering that only high quality RCTs examined this question, however, five showed a benefit,[5,17,27–29] and only one did not.[18] Therefore, reasonably consistent level 1 evidence indicates that separation anxiety is ameliorated by oral midazolam. The less well designed studies were more variable in their results.

TABLE II Summary of study outcome findings

Ref #	*Separation anxiety*	*Induction anxiety*	*Awakening*	*Emergence delirium*	*Recovery time*	*Long term behaviour*	*CEBM*
1	Beneficial with 0.75 mg·kg^{-1}	Beneficial with 0.5 & 0.75 mg·kg^{-1}	No effect		No effect		2b
2		No effect	No effect				2b
3		Beneficial with 0.5 mg·kg^{-1}	Delayed		PACU delay		2b
4	No effect	Beneficial	No effect		No effect		2b
5	Beneficial with 0.5, 0.75 & 1.0 mg·kg^{-1}	Beneficial with 0.5, 0.75 & 1.0 mg·kg^{-1}	No effect		No effect		1b
6						Beneficial for 2 weeks	2b
7	No effect	Beneficial			No effect		2b
8		Beneficial	Delayed		Discharge delay	Beneficial for 2 weeks	2b
9		Beneficial	No effect		No effect		1b
10		Beneficial					1b
11		No effect	Delayed	No effect	Discharge delay		2b
12	No effect	Uncertain					2b
13		No effect			No effect		2b
14	Beneficial	No effect	No effect				2b
15	No effect	No effect	Delayed		Discharge delay		2b
16		Beneficial			No effect	Detrimental for 1 week	2b
17	Beneficial	Beneficial	No effect	No effect	No effect	No effect at 2 weeks	1b
18	No effect	Beneficial with 0.5 & 0.75 mg·kg^{-1}	No effect	No effect	No effect		1b
19						Beneficial for 1 week	1b
20			Delayed	No effect	Discharge delay		1b
21			Delayed	Beneficial with sevo only	PACU delay		2b
22			Delayed	Detrimental	No effect		1b
23		Beneficial			No effect		1b
24	Beneficial	No effect	No effect		No effect		2b
25	No effect			Beneficial	No effect		2b
26		Beneficial	No effect		No effect		1b
27	Beneficial	Beneficial					1b
28	Beneficial	Beneficial					1b
29	Beneficial with 0.25 & 0.5 mg·kg^{-1}	Beneficial with 0.25 & 0.5 mg·kg^{-1}	No effect	No effect	No effect	No effect at 2 weeks	1b
30		Beneficial					1b

CEBM = Centre for Evidence-Based Medicine; sevo = sevoflurane; PACU = postanesthesia care unit.

Induction anxiety

Induction anxiety was evaluated in 24 studies. Of these, 17 showed a reduction in induction anxiety with midazolam, while seven others did not show a statistically significant benefit or were uncertain. When considering the 11 high quality RCTs that examined this question, all showed a benefit.[5,9,10,17,18,23,26–30] Accordingly, very consistent level 1 evidence indicates that induction anxiety is ameliorated by oral midazolam. Again, the less well designed studies were more variable in their results.

Emergence agitation (EA)

Eight studies addressed EA, or some equivalent phenomenon, such as "postoperative confusion". Of these eight studies, only two showed a reduction in EA with midazolam premedication,[21,25] one of which demonstrated a benefit only with sevoflurane anesthesia.[21] One study provided evidence that midazolam increases the incidence of EA.[22] Five of these studies[17,18,20,22,29] were of good quality, and none showed a benefit. Accordingly, there is no consistent evidence to suggest that midazolam premedication decreases the incidence of EA.

Recovery times

Eighteen studies evaluated emergence or awakening times. Of these, seven showed a delay in emergence, however the delay was usually quite brief. Of the eight high quality studies, only two demonstrated a delay in emergence.[20,22]

Discharge from either PACU or the institution was measured in 21 studies. Of these, just two showed a delay from PACU[3,21] and four showed a delay from the institution.[8,11,15,20] Of the nine high quality studies which evaluated this outcome, only one[20] showed a delay in discharge. The studies therefore provide little evidence to suggest a significant delay in recovery in midazolam-premedicated children.

Longer term outcomes

Six studies evaluated behavioural outcomes for a period of a week or more following anesthesia. Parents or guardians completed questionnaires that evaluated such behavioural dysfunction as nightmares, temper tantrums, and bed wetting. Of these six studies, three showed a reduction in negative behaviours during the first two postoperative weeks.[6,8,19] One study demonstrated worse behavioural outcomes at one week in the midazolam-treated group.[16] Three of these six studies were rated to be of high quality, with only one showing a benefit.[19] This well-conducted study showed a benefit for the first postoperative week only.[19] Accordingly, the data addressing the issue of behavioural outcomes in the first few weeks postoperatively is inconsistent.

Dose and timing

Five studies[1,3,5,18,29] evaluated different doses of midazolam, ranging from 0.1 $mg \cdot kg^{-1}$ – 1 $mg \cdot kg^{-1}$. The consensus of opinion from these studies is that a midazolam dose of 0.5 $mg \cdot kg^{-1}$ *po* is required to produce consistent preoperative anxiolysis in children < 12 yr. Increasing the dose to 0.75 $mg \cdot kg^{-1}$ or even 1 $mg \cdot kg^{-1}$ does not increase the anxiolytic benefit, and may cause ataxia preoperatively,[5] or prolonged sedation postoperatively. Other published studies examine different doses of oral midazolam, but unless a placebo or control group was included, these studies were not included in this review.

The studies varied considerably with respect to the timing of midazolam administration, ranging from ten minutes to two hours preoperatively. Some studies allowed for a considerable range in the timing. The most frequently used interval prior to separation or induction was 20–30 min. As there were often other variables at play (e.g., dosing, induction technique), it was not possible to determine from these papers what the optimal time for administration should be, although studies that have specifically examined this question suggest that the interval can be quite short (10–30 min preoperatively).

Patient selection

One study[30] addressed the issue of patient selection prior to the use of oral midazolam. This study demonstrated that children with high baseline levels of anxiety benefit the most from midazolam premedication, however high levels of trait impulsivity may contraindicate the use of midazolam as a preoperative medication. Easy, reliable ways of determining these psychological types need to be developed.

Limitations of this EBCU

The clinical question under consideration was addressed using the EBCU format of the *Journal*. There are other strategies that may be applied in order to answer a clinical question, such as meta-analysis. Meta-analyses have the advantage of being able to increase the statistical power of multiple studies, however they are limited by the quality of the science of the individual studies. In this particular situation, there was much variability in study design, and poor control of numerous confounding factors in many of the studies. We felt therefore that the EBCU format would be particularly suitable to provide a structured evidence-based expert opinion on the topic.

In determining whether a RCT was of good or poor quality, the three reviewers assessed numerous aspects of study design including, but not limited to, the confidence intervals, power analysis/sample size calculation, standardization of anesthesia and surgery, validation of the anxiety scoring system and standardization of other factors, such as parental presence at induction. There are published assessment tools, such as the Jadad score,[32] that address the quality of RCTs, however these are generally limited to certain aspects of study design. For example, the Jadad score only assesses studies on the basis of randomization, blinding and withdrawals/dropouts. Furthermore, the Centre for Evidence-Based Medicine does not have absolute criteria for grading the quality of RCTs. We elected therefore to use a broader, albeit less structured, evaluation of quality.

Conclusions

When considering the cumulative data, it must be remembered that several studies did not include a sample size estimation, standardized methodology, or a validated anxiety scoring system. With some of the sample sizes being as small as 12, the possibility of type 2 statistical errors cannot be excluded. Despite these limitations, several conclusions can be drawn.

Overall, there is evidence that premedication with oral midazolam reduces anxiety in children, both at separation from parents or guardians, and particu-

larly at induction of anesthesia. There is no consistent evidence, however, to indicate that the incidence of emergence agitation is significantly moderated. Awakening times appear to be delayed minimally, and there is inconsistent evidence that discharge times are prolonged by the use of midazolam premedication. There is conflicting evidence suggesting a benefit in terms of behavioural changes for the first few weeks postoperatively.

Given the modest size of all the studies evaluated, the safety of oral midazolam premedication cannot be predicted with certainty. Hhowever, in healthy children at least, there are no reports of serious side-effects in the literature reviewed. More research needs to be done to further determine which children would benefit most from this intervention.

Recommendations

Premedication with midazolam 0.5 $mg \cdot kg^{-1}$ *po* administered 20–30 min preoperatively, is effective in reducing both separation and induction anxiety in children (grade A recommendation), with minimal effect on recovery times. Oral midazolam premedication may be considered either routinely, or in children who display high levels of baseline anxiety preoperatively.

There is insufficient evidence at this time to recommend preoperative midazolam as a means of improving behavioural outcomes either in the PACU or for the first few weeks postoperatively. Furthermore, the efficacy and safety of oral midazolam premedication in medically compromised children has not been addressed.

APPENDIX Centre for evidence-based medicine criteria

Levels of evidence for studies concerning therapy or harm

1a Systematic review of RCT's (with homogeneity)
1b Individual RCT (with narrow confidence intervals)
1c All or none study
2a Systematic review of cohort studies (with homogeneity)
2b Individual cohort study, or poor quality RCT
2c Outcomes research, or ecological survey
3a Systematic review of case control studies (with homogeneity)
3b Individual case-control study
4 Case-series, poor quality cohort study, or poor quality case-control study
5 Expert opinion without explicit critical appraisal, or based upon physiology, bench research or "first principles"

Grades of recommendation

A Consistent level 1 studies
B Consistent level 2 or 3 studies
Extrapolations from level 1 studies
C Level 4 studies
Extrapolations from level 2 or 3 studies
D Level 5 evidence
Troublingly inconsistent or inconclusive studies of any level

RCT = randomized controlled trial.

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