Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies

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Background: Premedication is considered important in pediatric anesthesia. Benzodiazepines are the most commonly used premedication agents. Clonidine, an α2 adrenoceptor agonist, is gaining popularity among anesthesiologists. The goal of the present study was to perform a meta-analysis of studies comparing premedication with clonidine to benzodiazepines.

Methods: A comprehensive literature search was conducted to identify clinical trials focusing on the comparison of clonidine and benzodiazepines for premedication in children. Six reviewers independently assessed each study to meet the inclusion criteria and extracted data. Original data from each trial were combined to calculate the pooled odds ratio (OR) or the mean differences (MD), 95% confidence intervals [95% CI] and statistical heterogeneity were accessed.

Results: Ten publications fulfilling the inclusion criteria were found. Premedication with clonidine, in comparison with midazolam, exhibited a superior effect on sedation at induction (OR = 0.49 [0.27, 0.89]), decreased the incidence of emergence agitation (OR = 0.25 [0.11, 0.58]) and produced a more effective early post-operative analgesia (OR = 0.33 [0.21, 0.58]). Compared with diazepam, clonidine was superior in preventing post-operative nausea and vomiting (PONV).

Discussion: Premedication with clonidine is superior to midazolam in producing sedation, decreasing post-operative pain and emergence agitation. However, the superiority of clonidine for PONV prevention remains unclear while other factors such as nausea prevention might interfere with this result.

Accepted for publication 13 December 2009

PREMEDICATION before anesthesia is considered as an important stage in the process of anesthesia. The goals are to produce anxiolysis, sedation, amnesia, analgesia, salivation reduction, vagolysis, sympatholysis, to reduce gastric secretion and acidity and to prevent post-operative nausea and vomiting (PONV).

Benzodiazepines are the most commonly used premedication agents in children. They produce anxiolysis, sedation, amnesia and reduce PONV. Despite their efficacy in the treatment of emergence agitation, midazolam premedication has not been reported to prevent it. Impaired post-operative cognitive function has been reported after midazolam premedication in children.

The α2 adrenoceptor agonist (α2aa) clonidine has been shown to exhibit anesthetic, sedative, sympatholytic and analgesic properties.

Despite the clinical trials and reviews that have focused on the comparison between premedication with clonidine in comparison with benzodiazepines, no quantitative literature analysis has been published.

The goal of the present study was to perform a meta-analysis of the published studies comparing premedication with either clonidine or benzodiazepines to identify the most efficient drug from criteria used to define the ideal premedication.

Material and methods

Bibliographic search and analysis
We conducted this meta-analysis according to the guidelines of the Cochrane Handbook for systematic reviews of intervention and the QUORUM statements.

1http://www.cochrane-handbook.org/
Literature databases included Pubmed and Embase. The following queries were used: ‘premedication, and clonidine and midazolam and benzodiazepines and children or infant.’ Only English articles were considered. The date of the most recent search was April 2009.

The articles obtained from these queries were independently analyzed by six anesthesiologists and those meeting the following criteria were included in the analysis: comparison between clonidine and benzodiazepines for premedication, randomized-controlled study, double-blinded and standardized anesthesia and analgesia protocol. A manual search of the references found in the selected reviews was also performed.

Data considered were: sedation at induction, emergence agitation, post-operative pain during the first 120 post-operative minutes, PONV, and duration of emergence and stay in the post-operative care unit (PACU). When conflicting results were found, two independent anesthesiologists checked the article.

Statistical analysis
Statistical analysis was performed using the Review Manager 5 software (RevMan 5, The Cochrane Collaboration, Oxford, UK). When original data were expressed as continuous variables, meta-analysis was performed using the mean difference (MD) or the standardized mean difference (SMD) computed by a fixed- or a random-effect models. In all other cases, the analysis of the incidence of outcomes was performed using the odds ratio (OR) computed using the fixed or the random models of the Mantel–Haenszel method. Numbers needed to treat (and [95% confidence interval, CI]) were also calculated for each outcome according to the formula: NNT = (1 – (PEER × (1 – OR)))/((PEER × (1 – PEER) × (1 – OR)), where PEER represents the Patient Expected Event Rate (overall percentage of the event in the benzodiazepine group). The NNT is the number of patients who need to be treated with clonidine in order to prevent one additional bad outcome.

In order to minimize published bias, some data transformations were necessary. First, data expressed as median, ranges were transformed as mean, standard deviation (SD) according to a method described previously. The lack of a method to convert median, interquartile ranges to means and SD led us to discard all data expressed in this way. For outcomes with mixed percentages and continuous results, the standardized mean ratio was first computed and then transformed as partial OR using the formulae: \[ \text{Ln}(\text{OR}) = 1.814 \times \text{SMR (Ln: logarithm)} \]. Partial Ln(OR), from data expressed as percentages, was calculated from OR and its 95% CI. The data were then entered as Ln(OR) and SD[LN(OR)]. The overall OR (and 95% CI) was finally computed with the inverse variance method.

Heterogeneity was assessed using \( I^2 \) statistics. This describes the percentage of the variability in effect estimates (OR, MD or SMD) that is due to heterogeneity rather than sampling error. According to the Cochrane review guidelines, an \( I^2 > 40\% \) and a \( P < 0.1 \) were considered as the threshold for heterogeneity and indicated subgroup analysis and the use of a random effect in meta-analysis computation. Subgroup analysis was performed according to the factors influencing the different outcomes such as PONV prevention or pain treatments in the case of the preventive effect of premedication on these two outcomes. Results are expressed as OR, MD or SMD [95% CI, \( \hat{I}^2 \), \( P \) value of heterogeneity.

Where studies addressed more than one intervention group, each was considered as a study and compared with the control group. Finally, to avoid computation problems related to zero effectives, 1 was added to all groups.

Bias related to unpublished studies was assessed for analysis aggregating at least 10 studies using a funnel plot and the Begg–Mazumdar test. This test explores the interdependence of variance and effect size.

Results
Using the selected criteria, 167 articles were identified, of which 13 were appropriate controlled trails. Three of these were discarded because of the use of dexmedetomidine, study of the effects of clonidine during induction and absence of clinical outcomes, leaving 10 relevant publications for further analysis. The details of the selection process are summarized in Fig. 1, and a description of analyzed articles is summarized in Table 1.
Sedation at anesthesia induction
Midazolam was used in two studies\textsuperscript{11,19} (including three arms) and was less effective than clonidine in producing sedation (OR = 0.49 [0.27, 0.89], $I^2 = 35\%$, $P = 0.22$). In contrast, no difference was found between clonidine and diazepam\textsuperscript{15,16,18} (OR = 1.19 [0.37, 3.85], $I^2 = 84\%$, $P < 0.0001$). NNT between clonidine and midazolam for this outcome was 8, with a 95\% CI ranging from 4 to 56.

Emergence agitation
This analysis involved two studies including a total of three intervention arms.\textsuperscript{11,19} All studies compared premedication with clonidine with that using midazolam. The incidence of emergence agitation was statistically lower in the clonidine groups (OR = 0.25 [0.11, 0.58], $I^2 = 0\%$, $P = 0.52$). NNT was 6 [5–13].

Post-operative pain
Early post-operative pain intensity, based on the first 120 post-operative minutes, was reported in three studies (with an total of four arms) comparing clonidine with midazolam.\textsuperscript{12,19,20} Clonidine decreased the post-operative pain scores (OR = 0.33 [0.21, 0.52], $I^2 = 0\%$, $P = 0.53$). NNT for this outcome was 4 [3–8].

Duration of emergence and PACU stay
The duration of emergence from anesthesia (time from anesthesia discontinuation to extubation) was analyzed in two studies (three arms)\textsuperscript{13,19} reporting clonidine equivalent to midazolam (MD (min) = 0.08 [−0.46, 0.63], $I^2 = 69\%$, $P = 0.04$). The duration of PACU stay was reported in two studies (two arms)\textsuperscript{13,20}. No difference was found between the two agents (MD (min) = −9.00 [−18.81, 0.81], $I^2 = 0\%$, $P = 0.1$).

PONV
The effect of clonidine on PONV was analyzed from three studies comparing clonidine with midazolam or diazepam.\textsuperscript{13,14,17} Analyzing studies in which diazepam was used and PONV not prevented\textsuperscript{14,17} found clonidine to exhibit a superior effect on PONV prevention (OR = 0.34 [0.13, 0.94], $I^2 = 46\%$, $P = 0.16$). NNT of this subgroup analysis was 5 [3–72].

Only one study\textsuperscript{13} reported the comparative incidence of PONV for clonidine and midazolam and found no differences between these two agents (OR = 1.12 [0.46, 2.7]).

Bias was not assessed because of the limited number (below 10) of studies included in each analysis.

Discussion
The main findings of this meta-analysis can be summarized as follows: premedication with clonidine produces more satisfactory levels of sedation at induction, decreases emergence agitation and produces more effective early post-operative analgesia, when compared with midazolam. Furthermore, in comparison with diazepam, clonidine was more effective in PONV prevention.

Clonidine was found to be superior to midazolam in producing acceptable levels of sedation at induction. In contrast, the high heterogeneity of the comparison between clonidine and diazepam could not allow any valid conclusion regarding this outcome.

Interestingly, the superiority of clonidine over benzodiazepines was mainly observed in the post-operative period. Clonidine was superior to mid-
<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>ASA status</th>
<th>Surgeries</th>
<th>Dose of clonidine (μg/kg)</th>
<th>Route and timing of administration (mn)</th>
<th>Dose of benzodiazepines (mg/kg)</th>
<th>Route and timing of administration (mn)</th>
<th>Anesthetics</th>
<th>Perioperative Analgesia</th>
<th>Antiemetics</th>
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<td>Ibuprophen, LRA</td>
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<td>I</td>
<td>T&amp;A</td>
<td>5</td>
<td>R, 30–60</td>
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<td>I/II</td>
<td>T&amp;A</td>
<td>4</td>
<td>O, 90</td>
<td>M 0.5</td>
<td>O, 30</td>
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<td>acetaminophen+ Morphine</td>
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<td>4</td>
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<td>Sevoflurane</td>
<td>None</td>
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Characteristics of included studies: ages are expressed as years. Studies with more than one clonidine harm are labelled * and †. T&A, adenotonsillectomy; O, oral route; R, rectal route; LRA, locoregional analgesia.
azolam in improving post-operative pain relief and decreasing the incidence of emergence agitation. NNTs for these two outcomes indicate a clinically relevant effect. These post-operative effects of clonidine might result from their intraoperative and/or post-operative analgesic effect and their preventive effects against post-operative pain and emergence agitation. In addition, the short duration of studied surgery, together with clonidine’s relatively prolonged pharmacokinetic profile, may have favored clonidine.

Regarding PONV, clonidine had no overall preventive effect compared with midazolam or diazepam. However, in the three studies without pre-operative PONV prevention, clonidine exhibited a slight superiority over diazepam (CI for NNT: 3–72). In addition, the studies included in this analysis used diazepam instead of midazolam and studied strabismus surgery. The use of ondansetron plus dexamethazone in these studies might have influenced the overall results by blunting the superiority of clonidine. Finally, the high rate of PONV during strabismus surgery might have increased the statistical power of the comparison between clonidine and diazepam.

Some methodological considerations require discussion. Midazolam was used either orally or rectally at a 0.5 mg/kg dosage in all included studies. However, these routes of administration have been associated with low and variable bioavailability. This may produce an underdosage of this agent favoring clonidine. Excluding the study in which midazolam was given rectally did not influence the results of this meta-analysis.

All papers included in this meta-analysis studied minor and short-duration ambulatory surgery. Despite the sedative effects and long pharmacokinetic profile of clonidine, patients’ recovery and discharge have not been evaluated in the included studies. Consequently, no recommendation could be drawn concerning the use of clonidine during ambulatory surgery.

The techniques used to measure emergence agitation were another limitation of this meta-analysis. The validated pediatric anesthesia emergence delirium scale (PAED) was not used in the included studies. This may have introduced inaccuracy in the estimation of the true incidence of this effect in children. In addition, post-operative pain was only analyzed during the first 120 min of the post-operative period. This clearly limits the impact of this meta-analysis on the efficacy of clonidine on late post-operative pain reduction.

Multiple factors introduced heterogeneity in this meta-analysis: including anesthesia and analgesia protocols and evaluation methods for each outcome (pain scoring methods, emergence agitation evaluation). Sedation at induction (comparison between clonidine and diazepam), duration of emergence and PONV incidence were outcomes that demonstrated heterogeneity. Sedation at induction demonstrated the greatest heterogeneity precluding any conclusion regarding this result. The duration of emergence from anesthesia exhibited moderate heterogeneity. However, subgroup analysis was not possible as this outcome depends on the results of only two studies. Concerning PONV, a lower incidence was found when clonidine was compared with diazepam. However, these studies only included strabismus surgery that did not include PONV prophylaxis, leaving the role of the type of surgery and PONV prophylaxis in the case of clonidine unclear.

In conclusion, premedication with clonidine is superior to midazolam in terms of producing sedation, decreasing post-operative pain and emergence agitation. Compared with diazepam, clonidine was superior in terms of preventing PONV during strabismus surgery without PONV prophylaxis.

Acknowledgement

Conflict of interest: none.

References


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