Three Adjuncts to Anesthesia to Prevent Emergence Agitation in Pediatric Dentistry; a Pilot Study

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Citation

W Mckay, K Derdall, M Brahmania, C Nagle, I Hamilton, M Teekasingh. Three Adjuncts to Anesthesia to Prevent Emergence Agitation in Pediatric Dentistry; a Pilot Study. The Internet Journal of Anesthesiology. 2010 Volume 29 Number 1.

Abstract

PURPOSE A pilot study of adjuncts to anesthesia that decrease pain, tissue edema, and nausea intended to direct research into postoperative emergence agitation in children having dentistry under general anesthesia.

METHODS A blinded randomised controlled trial compared morphine/ meperidine, dexamethasone, granisetron, and a combination of the three to saline placebo. Primary outcome was incidence of emergence agitation in each group. Data was collected in the Post Anesthesia Care Unit, and at home next day.

RESULTS 205 subjects took part. The placebo group had more emergence agitation (18/40; 45% [95% confidence intervals 29 to 61%] compared to morphine (1/20; 5% [0.2 to 26%]; P = 0.004), but had less vomiting (6 [1.2 to 11] episodes) compared to morphine (51 episodes [37 to 65]; P < 0.0001). No other agent was efficacious. Of four patients with pain at home follow-up, only one had dental pain. Four patients were ill enough for their parents to seek medical attention. CONCLUSION Intravenous morphine 50 mcg kg\(^{-1}\) added to a vapour-based anesthetic prevented emergence agitation, but produced unacceptable vomiting. Other agents had no evident effect. A number of subjects had mild to moderately severe adverse events postoperatively. Pediatric dental care under general anesthesia is not entirely innocuous. Improvements to anesthesia care must still be sought.

IMPLICATION STATEMENT

Many children require dental care under general anesthesia. Post-operative emergence agitation, vomiting, pain, or distress is upsetting for child and parent, and can result in complications. This is a pilot study of anesthetic adjuncts with diverse properties given to promote smooth awakening. No promising agents were found.

INTRODUCTION

Small children with extensive carious dental disease require dental care under general anesthesia (GA) that often includes pulpotomies, stainless steel crowns and extractions. Although they could be expected to have little or no post-operative pain, aside from minor gum irritation from clamps, rubber dams, etc. their post-operative course is often marred by vomiting (35%),\(^1\) prolonged crying, and emergence agitation (EA - 18%).\(^2\) A number of pharmacologic adjuncts to general anesthesia have been systematically studied, with mixed results.\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\)

Children of the age (3 to 6years) commonly treated for carious disease under GA cannot articulate symptoms clearly. We wondered if they might be distressed by nausea, pain, or intra-oral post-traumatic edema causing abnormal tissue sensation perceived as discomfort.\(^12\) We hypothesised that intravenous granisetron (G) for nausea, morphine (M) for pain, dexamethasone (D) for tissue edema), or combination (C) of all three, would result in smoother emergence from dental care under general anesthesia in children than saline placebo, as measured by episodes of EA, vomiting, crying, appearing to suffer pain, or seeming distressed.

EA is a common side effect of general anesthesia in children that is not well understood, and was the primary outcome.\(^13\),\(^14\),\(^15\) We wondered if decreasing the perception of discomfort could ameliorate the sensations listed above to decrease the incidence of EA. The study was intended as a pilot, to guide a further dose-ranging study of the most promising of the drugs tried, and to allow for sample size calculation. In addition, we wished to document other symptoms such as pain, vomiting, and behaviour indicating distress, as a guide to providing informed consent to future patients.
METHOD

Study design. The study is a blinded, placebo-controlled, randomised trial, with concealment, of these drugs as adjuncts to GA for prevention of EA, in a tertiary care health sciences centre. Patients, parents (or their surrogates), healthcare workers, assessors and data enterers were blinded. Randomisation by computer-generated random-number table took place after recruitment, using opaque sealed envelopes containing the study drug allocation. Study drug was prepared by a physician not involved in the trial. Study drugs are all physically clear and transparent and cannot be distinguished in the syringe from saline, and all were mixed with saline to an identical volume. The study took place from 2004/06/11 to 2005/10/18.

The study consists of two parts. It was begun with halothane (Hal) as the anesthetic vapour but changed to sevoflurane (Sev) after recruiting 105 subjects because halothane was no longer available in Canada. A safety monitoring committee consisting of the non-assessing authors in camera decided to change morphine to meperidine at this time because morphine was causing an unacceptable incidence of vomiting postoperatively. Thus, the second half of the experiment used sevoflurane as the vapour, and meperidine as the analgesic. Vapour use was not blinded.

Subjects. Included were all children attending the University of Saskatchewan's Royal University Hospital Dental Clinic or College of Dentistry Dental Clinic for dental care under GA. This population was chosen because they encompass the ages known to suffer most often from EA. Excluded were those with allergy to any study or anesthetic drug, those with documented developmental delay, those whose parent or guardian was unable to give informed consent, and those who could not be reached by telephone the following day.

Study drugs and doses. Subjects were randomised to one of the following 5 arms, with drugs to be given in blinded fashion after induction: saline placebo (group S), narcotic: morphine 50 mcg kg\(^{-1}\) for the first half of the experiment, then meperidine 0.5 mg kg\(^{-1}\) (group N), or dexamethasone 150 mcg kg\(^{-1}\) (group D), or granisetron 40 mcg kg\(^{-1}\) (group G) or, or a combination of the three active drugs in half of the above doses (group C). Anesthetic technique. All subjects were given oral ibuprofen (liquid Advil\textsuperscript{®}) 10mg/kg in the waiting area, then administered a standard general anesthetic, using a mask induction of halothane or sevoflurane in equal parts nitrous oxide and oxygen, followed by placement of an intravenous (IV) catheter, intubated nasally after an IV dose of 2 mg/kg of propofol, then given maintenance anesthetic of halothane or sevoflurane in equal parts air and oxygen. All subjects got approximately 4ml/kg/h of 0.9-normal saline for the first 10kg body weight, 2ml/kg/h for the next 10kg, and 1ml/kg/h for additional weight, as was normal practice. If any arrhythmia occurred on halothane the vapour was changed to sevoflurane. Respiration was spontaneous or assisted as necessary. All had intraoperative regional or local infiltration by the dentists with lidocaine 2% with 1:100,000 epinephrine. Pain control thus followed accepted recommendations. Parents were present at induction and in PACU.

Measurements. Any of the following criteria, if present continuously for more than 5 minutes, were used to diagnose emergence agitation (EA): restlessness with non-purposeful movement; thrashing; incoherence; inconsolable crying; unresponsiveness although awake. These are liberal diagnostic criteria incorporating criteria from all the studies cited in the references. To assess validity of EA measurement, the Pediatric Anesthesia Emergence Delirium Scale (PAEDS) score was also applied in PACU to the group receiving sevoflurane. Episodes of vomiting in PACU were recorded.

At a follow-up telephone call the next day, we enquired about the child's wellbeing, pain, behaviour, vomiting, and any other complications using a standard script. We use the term "distress" to describe a child who was not behaving normally and appeared to be upset, unhappy, and/or uncomfortable at the home follow-up call. Unanswered calls were repeated daily at least three times.

Patient Safety. All of these drugs are approved for use in humans in Canada, and are commonly used in local practice. Interim analysis for safety was conducted after 100 subjects were recruited. When interim analysis showed an unacceptable incidence and severity of vomiting in the morphine group, the narcotic was changed to meperidine.

Statistical Analysis. Sample size calculation was used to determine numbers of subjects. With alpha = 0.05, and beta = 0.8, 40 subjects per group are needed if we assume a decrease in crying time of 10 minutes and use a conservative standard deviation of 15 minutes, based on an EA incidence of 0.18 and standard deviation of EA duration of 11 minutes.
Continuous variables were analysed by ANOVA, categorical variables by Chi-square, and ordinal data by ANOVA-on-ranks with alpha = 0.05. Counts were analysed by approximation to a Poisson distribution. Confidence intervals of proportions included continuity correction and were calculated with an on-line calculator. The strength of association of the PAEDS with EA was analysed by logistic regression. Because it is a pilot study, no corrections were made for multiple comparisons. Analysis was two-tailed and by intention to treat. Statistical analysis was done using Sigmastat® version 3.11 (Systat Software Inc, Chicago IL, USA).

RESULTS
Disposition of subjects is given in the CONCORD diagram, Figure 1. Demographics are listed in Table 1. The 38 subjects lost to next-day follow-up could not be reached by telephone. While 84% of the 167 parents responding to telephone follow-up reported completely normal behaviour next day, 11/167 (6.6% [3.5 to 11.8%]) reported symptoms more severe than merely listlessness or lack of appetite.

Figure 1
Figure 1 – CONCORD Diagram

Table 1 – Demographics (mean±S.D. or numbers female/male)

<table>
<thead>
<tr>
<th>Group</th>
<th>Hal</th>
<th>Sev</th>
<th>S</th>
<th>N</th>
<th>G</th>
<th>D</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>54±20</td>
<td>51±20</td>
<td>51±20</td>
<td>54±17</td>
<td>52±20</td>
<td>54±24</td>
<td>52±19</td>
</tr>
<tr>
<td>Geofa (Fm)</td>
<td>44±61</td>
<td>58±42</td>
<td>58±42</td>
<td>58±42</td>
<td>58±42</td>
<td>58±42</td>
<td>58±42</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20±5.1</td>
<td>19±4.9</td>
<td>19±4.9</td>
<td>19±4.9</td>
<td>19±4.9</td>
<td>19±4.9</td>
<td>19±4.9</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>76±24</td>
<td>71±20</td>
<td>70±17</td>
<td>71±23</td>
<td>75±26</td>
<td>73±26</td>
<td>77±23</td>
</tr>
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</table>


Emergence agitation. There was no difference in incidence of EA between vapours (EA/no EA: halothane 37/68; sevoflurane 42/58; P = 0.39). Incidence of EA is tabulated in Table 3. In the study as a whole, the narcotic group had less EA than the other groups (P = 0.03). Comparing Morphine, meperidine, and saline placebo, morphine was significantly more efficacious (P = 0.004). Five subjects had arrhythmias.
on halothane and were switched to sevoflurane; all arrhythmias resolved rapidly with no further intervention.

**Figure 3**

Table 2 – Emergence Agitation incidence (%) [95%CI of %]

<table>
<thead>
<tr>
<th></th>
<th>Hal</th>
<th>Sev</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>37/105 (5)</td>
<td>42/100 (42)</td>
<td>0.30</td>
</tr>
<tr>
<td>18/40(45)</td>
<td>8/42(19)*</td>
<td>14/41(34)</td>
<td>0.03</td>
</tr>
<tr>
<td>19/41(46)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>36/100 (36)</td>
<td>40/100 (40)</td>
<td>0.70</td>
</tr>
<tr>
<td>18/40(45)</td>
<td>8/42(19)</td>
<td>14/41(34)</td>
<td>0.03</td>
</tr>
<tr>
<td>19/41(46)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>20/44(45)</td>
<td>20/44(45)</td>
<td>0.90</td>
</tr>
<tr>
<td>20/44(45)</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>20/44(45)</td>
<td>20/44(45)</td>
<td>0.90</td>
</tr>
<tr>
<td>20/44(45)</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>19/41(46)</td>
<td>19/41(46)</td>
<td>0.90</td>
</tr>
<tr>
<td>19/41(46)</td>
<td>0.90</td>
<td></td>
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</tbody>
</table>

*significantly different from other treatments in the row


The PAEDS scoring system (see Figure 2) was highly predictive of EA as we measured it (odds ratio of PAEDS score >10 predicting EA by our scoring system: 2.1[1.6 to 2.8]; odds ratio of PAEDS score >15, 12.3[4.3 to 47.2]; linear R = 0.7; P < 0.0001 for both constant and coefficient).

**Figure 4**

Figure 2. Distribution of PAEDS scores and EA numbers. X-axis: PAEDS score; White columns: frequency of PAEDS score; black columns: frequency of EA.

Vomiting. Vomiting data is summarised in Table 4, where “incidence of vomiting” refers to the number of subjects that vomited, and “counts of vomiting episodes” refers to the total number of times that subjects vomited, and is an indication of severity of vomiting. Halothane caused more-severe vomiting than sevoflurane. The narcotic group suffered more and more-severe vomiting than the other groups.

**DISCUSSION**

Almost everyone approached agreed to be in the study. Thus, such studies are feasible in this population. Thirty-eight subjects were lost to home follow-up. Many of our subjects live in remote Northern villages with limited telephone service, and rely on friends and relatives for use of a telephone. Thus, while all had given us a telephone number, for some, the telephone was not in their home, and they were not easily found.

Emergence agitation. Morphine prevented EA, but had an unacceptable incidence of vomiting. No other agent appeared to be efficacious. The PAEDS score correlates very
well with the criteria for EA used in this study. The half-dose of morphine in group C neither prevented EA, nor provoked vomiting. That the vapour used had no effect on EA is at odds with other studies that found a difference, but is in agreement with five studies quoted in Moore’s review.

Vomiting. Many of our patients travel long distances, with airplane or long car rides home. Parents gave us the impression (exact numbers not kept) that it was on the way home that most subjects vomited. Halothane may or may not provoke vomiting more than sevoflurane; it was paired with morphine, while sevoflurane was paired with meperidine.

Pain. Significant pain in PACU is rare with this kind of dental work at this age, and with this regimen of pre-op medications and intra-operative regional anesthesia. Only one child had oral (post-surgical) pain at home follow-up. Two had abdominal pain and one headache. Thus, while the dental procedure does not appear to be painful, there is room for improvement in anesthetic techniques. There was no evident pattern of relationship of pain to any experimental intervention.

Distress. Most distress was mild, but one parent decided to seek medical attention. We could discern no apparent pattern pointing to cause and effect of treatments and distress.

Weaknesses of the study. The study did not use a consistent vapour because of loss of halothane supply. Another weakness is shared with the overwhelming majority of randomised controlled trials of drugs in anesthesia: for logistical reasons, we used single doses instead of a dose-ranging study. Thus our conclusions are true only for the doses used.

Drug doses. These doses of morphine and of meperidine have been found anecdotally in our institution to prevent agitation without compromising respiration. Meperidine has been shown to diminish postoperative nausea and vomiting in this dose. The dose of dexamethasone was chosen as a compromise between the doses of 100ug/kg reported in one recent study, and 500ug/kg reported in another, and is the dose recommended in a consensus paper. The dose of granisetron is from published studies of post-operative vomiting. Because the adult post-operative nausea and vomiting literature suggests that combinations of drugs are more effective, even in smaller doses, an additional group was given a combination of a half-dose of all of the active drugs. Rational for the half dose is the expectation that it may result in fewer side effects with the same or greater benefits.

Summary and future directions. This was intended as a pilot study to suggest what types of drugs in these categories should be studied further, and which should probably be dismissed as unlikely to be useful. Unfortunately, none of the drugs studied clearly point the way to further studies. Importantly, the finding that 11/167 (6.6%) of our subjects had side effects that were more severe than listlessness or lack of appetite is probably generalisable to pediatric patients having dental work under general anesthesia. This points the way to the need for improvement in care and may be helpful in providing informed consent to parents.

ACKNOWLEDGEMENTS

This study was funded by a grant from The Royal University Hospital Foundation. We gratefully acknowledge the expert and efficient work of Sally Tufts, RN, who conducted much of the recruitment and data collection.

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