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Two-agent analgesia versus acetaminophen in children having bilateral myringotomies and tubes surgery

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Summary

Objectives—The objective of this study was to determine whether the incidence of emergence agitation (EA) can be reduced by adding an additional, faster onset, non-IV analgesic, intranasal fentanyl or intramuscular (im) ketorolac to rectal acetaminophen.

Aim—To compare the incidence of EA after analgesia with two agents vs acetaminophen alone in pediatric patients after bilateral myringotomy procedures (BM&T).

Background—Anesthesia for BM&T is usually performed with volatile anesthetics as a single agent without securing intravenous access. The anesthetic agent most commonly used is sevoflurane; however, EA has been reported in up to 67% of patients. Emergence agitation is distressing for parents, can impair the ability of nursing staff to adequately monitor the child, and can result in a child injuring him/herself if it is severe.

Methods/Materials—A standardized anesthetic was used with oral midazolam premedication and sevoflurane for induction, and maintenance of anesthesia. All patients received 40 mg·kg⁻¹ rectal acetaminophen, group 1 received acetaminophen alone, group 2 received acetaminophen and 1 mcg·kg⁻¹ of intranasal fentanyl, and group 3 received acetaminophen and 1 mg·kg⁻¹ of intramuscular ketorolac. Incidence of EA was compared using chi-square test between the acetaminophen group alone vs the two-agent analgesia groups combined.

Results—There were no differences in demographic and clinical characteristics between the two groups. There were no statistically significant differences between the three groups for the incidence of EA at any time point during recovery from anesthesia nor were there any significant differences in pain scores or side effects. No significant side effects because of the administration of a second analgesic agent were reported.

Conclusions—We conclude that two-agent analgesia is not superior to acetaminophen alone for decreasing the incidence of EA after inhalation anesthesia with sevoflurane for BM&T surgery. Our overall incidence of EA was low compared to previous studies, which could potentially have decreased our ability to detect differences between groups.

Keywords

ear tube surgery; children; postoperative analgesia; emergence agitation; intranasal fentanyl; intramuscular ketorolac

Introduction

One frequent surgery carried out in pediatric patients is bilateral myringotomies with tube placement (BM&T). Because of the brevity of the procedure, anesthesia is often accomplished via inhalational induction and maintenance with a face mask and spontaneous ventilation with volatile agents, without securing intravenous access. The anesthetic agent most commonly used is sevoflurane; however, emergence agitation (EA) has been reported in up to 67% of patients receiving it as the sole anesthetic for this procedure (1). Emergence agitation is distressing for parents, can impair the ability of nursing staff adequately to monitor the child, and can result in a child injuring him/herself if it is severe.

Multiple factors such as type of anesthetic agent, age, and inadequate analgesia have been suggested as contributors to EA. Postoperative analgesia has been found necessary in up to 70% of children undergoing BM&T (2). As intravenous (IV) catheterization is uncommon for this procedure, in North America, alternative routes to administer analgesics are needed.

The present study compares the effect of three non-IV analgesic regimens on the incidence of agitation during emergence from anesthesia for BM&T procedures in young children to explore what part of agitation is because of inadequate analgesia.

Methods

After Institutional Review Board (IRB) approval, a double-blind, three-arm, randomized controlled trial was carried out, comparing rectal acetaminophen alone to a combination of rectal acetaminophen plus intramuscular (im) ketorolac or intranasal fentanyl. Enrollment began in 2003 and closed in 2008. An investigational new drug application was obtained from the Federal Drug Administration for the use of intranasal fentanyl in this population.

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A sample size of 255 patients was estimated to detect a 20% difference in the proportion of children showing agitation with acetaminophen alone to those receiving two analgesics, with an $\alpha = 0.05$ and power of 90%.

Healthy children ASA1 and 2 scheduled for BM&T surgery (aged 1–5 years) were eligible for the study. Exclusion criteria included children having any procedure in addition to the

BM&T, chronic medical issues (ASA class 3 or higher), developmental delay making agitation and pain scoring harder, or any allergy or contraindication to study medications. Children receiving opioid medications or nonsteroidal analgesics chronically were also excluded.

After written informed parental consent was obtained, children were randomized to one of three groups for analgesia: rectal acetaminophen 40 mg·kg⁻¹, rectal acetaminophen 40 mg·kg⁻¹ plus intramuscular ketorolac 1 mg·kg⁻¹, or rectal acetaminophen 40 mg·kg⁻¹ plus intranasal fentanyl 1 mcg·kg⁻¹. Standard randomization was carried out by the pharmacy, who then supplied sequentially numbered envelopes with the group assignment. The envelopes were handed to the anesthesia provider but the observer remained blinded as to group assignment.

All patients received a standardized anesthetic consisting of oral premedication with midazolam 0.5 mg·kg⁻¹, inhalation induction, and maintenance anesthesia with sevoflurane/N₂O/O₂ by mask. The study drugs were administered after induction, prior to surgery start, by the unblinded anesthesiologist taking care of the patient. All children had a bandaid placed on the anterior thigh to maintain blinding to group assignment for the postoperative observer, who was not present in the operating room.

Agitation and pain assessments were carried out by a blinded observer in the post anesthesia care unit (PACU). For the purpose of the study, the postoperative period is defined as the time spent in PACU until discharge from the hospital. In our institution, this time is spent in two separate areas: early recovery (Phase I) where patients are under close monitoring immediately after surgery and parents are not present and late recovery (Phase II) where patients reunite with their parents and are monitored for pain and oral intake until discharge.

Postoperative agitation was measured using a 4-point sedation scale (1 = calm, quiet, 2 = crying but can be consoled, 3 = crying, cannot be consoled, and 4 = agitated and thrashing around) (3). Pain assessment was carried out using a behavioral pain scale, the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (4). Both measurements were taken at first arousal in phase I, prior to discharge to phase II recovery and prior to discharge from phase II recovery. On discharge from phase II, the occurrence of nasal irritation/pain, rhinorrhea, nausea/vomiting as well as bruising at the site of ketorolac injection was assessed. Assessment of these was also carried out during a postoperative telephone call the day following surgery.

Patient demographic characteristics, duration of surgery, time in Phase I and II PACU areas were summarized with descriptive statistics (means and standard deviations or percentages, as appropriate). The primary outcome measure was the occurrence of an agitation score of 3 or greater at arousal, by transfer from Phase I to Phase II PACU, or by discharge from Phase II PACU. Proportion estimates and their accompanying 95% exact binomial confidence intervals are provided for this outcome by study group. The primary analysis was conducted using chi-square test. In addition, the ordinal agitation score and pain score observations were compared between groups at each time point separately using Kruskal–Wallis tests. The occurrence of nasal irritation/pain, rhinorrhea and nausea/vomiting was tabulated by

study group and compared using chi-square tests, or if the event type was too rare, using a Fisher's exact test. The incidence of bruising at the injection site was summarized for the ketorolac group only.

Study accrual was closed early. Decreasing use of oral midazolam over the study period led to the decreasing numbers of eligible patients. The original intent was to ensure 90% power to detect a 20% or greater difference in agitation between the group that received acetaminophen alone and the group that received two agents for analgesia. As the study enrollment was close to the planned enrollment, the actual power of the study is 86%, which is 4% less than that calculated with the original design.

Results

A total of 229 subjects were enrolled in the study. One enrollee was determined by the treating surgeon to need an additional surgical procedure; therefore, the patient was ineligible and was withdrawn from the study before the start of surgery. All analyses relate to the remaining 228 eligible subjects.

Of the 228 subjects enrolled, an equal number of patients were allocated to each group: 77 to the acetaminophen group (A), 75 to the acetaminophen + fentanyl (AF) group, and 76 to the acetaminophen + ketorolac (AK) group. There were no statistical differences in age, weight, and gender between groups. Duration of surgery and time in early and late recovery areas were also similar between groups (Table 1).

The primary outcome for the study was defined as a dichotomous indicator, a maximum agitation score of ≥ 3 or an agitation score of <3 . The proportion of patients with an agitation score ≥ 3 was not significantly different at any time point (arousal, transfer from Phase I to Phase II PACU and discharge from Phase II PACU) when compared between the acetaminophen group (A) vs the combined groups AF and AK. A supplementary analysis (not shown) evaluating differences in the proportion of subjects with a maximum agitation score ≥ 3 among all three treatments as separate groups was also not statistically significant.

Analysis of agitation scale scores in their original 1–4 ordinal scale (i.e., not dichotomized to ≥ 3 vs <3) and pain scores at each time point (arousal, transfer from Phase I to Phase II PACU and discharge from Phase II PACU) is also not statistically significantly different between groups. Means and standard deviation for pain and agitation scale scores are presented (Table 2). Medians were also computed. All groups had identical median agitation scores at each time point (median = 1). Pain score medians were also identical across all groups at arousal (median = 7) and at transfer (median = 6). At discharge, the median pain score was 5.5 in the group that received ketorolac and 6 in each of the other two groups.

Safety/side effects for intramuscular ketorolac administration and intranasal fentanyl administration were evaluated (Table 3). Bruising at the injection site was noted in 4 of 69 ketorolac subjects (6%) assessed at discharge. The proportion of subjects for whom voiding prior to discharge was documented was similar across groups (58% for acetaminophen only; 57% for AF and 62% for AK). For those who had not voided prior to discharge from phase II, voiding was confirmed at their postoperative phone call the next day. The average value

of subjects' minimum O₂ saturations recorded in Phase I and II PACU was also very similar between groups (means >98% for all groups during Phase I; means >99% for all groups during Phase II).

Discussion

Emergence agitation is a frequent and distressing occurrence after BM&T surgery. Although not considered a very painful procedure, in a retrospective review of their cases, Orobello *et al.* (2) found that up to 70% had either elevation of blood pressure, heart rate, or behavioral signs or complaints of pain. Many studies since have sought to determine the optimum anesthetic and analgesic regimen for this surgery. We studied the incidence of EA in children managed with three different analgesic regimens and found all were successful in keeping the overall EA incidence low (13–18%). Furthermore, when agitation scores were analyzed separately at each time point, we did not find any significant differences; specifically, when looking only at agitation scale scores at arousal, possibly the most representative for evaluating EA, no differences were found between groups.

Is emergence delirium caused by untreated pain?

Rectal acetaminophen absorption is reported as highly variable with an onset time of about 45–60 min (5). Our hypothesis therefore was that if EA is related to inadequately treated early postoperative pain, then adding an agent with faster onset would result in better early postoperative analgesia and consequently less EA. The two agents that we chose were intranasal fentanyl which reaches a therapeutic plasma level within 10 min (6) and intramuscular ketorolac, with an onset time of 20–25 min (7) in previous studies, a timeframe that fits this short anesthetic/surgical procedure.

Ketorolac

Several studies have suggested that ketorolac is a useful analgesic for this surgery. Pappas *et al.* (8) studied 120 children, aged 6 months to 6 years having BM&T surgery. There were four groups, oral acetaminophen alone, oral acetaminophen with codeine given preoperatively, butorphanol intranasally, immediately after anesthesia induction, or intramuscular ketorolac immediately after induction. Rescue analgesics were needed in 43 (codeine group), 31 (butorphanol), and 27% (ketorolac) of children vs 70% in the acetaminophen only group. The codeine and butorphanol groups had a 23–25% incidence of vomiting, making the ketorolac group superior overall. Davis *et al.* (9) found that intravenous ketorolac improved the emergence period in 200 children having BM&T surgery under halothane or sevoflurane anesthesia. Several years ago, Watcha *et al.* (3), in a study randomizing 90 children having BM&T surgery to oral acetaminophen 10 mg·kg⁻¹ or ketorolac 1 mg·kg⁻¹, found lower pain scores in the ketorolac group in the early postoperative period. However, not all investigators have been able to show the same benefit with ketorolac. Bean-Lijewski and Stinson (10) reported in 132 children randomized to receive oral acetaminophen or ketorolac before BM&T surgery. Only minimal improvement in pain scores at 5 and 10 min was seen in children treated with oral ketorolac compared to oral acetaminophen. Time to hospital discharge was no different.

Intranasal fentanyl

Galinkin (6) and Finkel (11) have reported the use of intranasal fentanyl in children having BM&T surgery. Galinkin *et al.* (6) undertook a two-phase study of intranasal fentanyl 2 mcg·kg⁻¹ in children having BM&T surgery with halothane or sevoflurane inhalational anesthesia. Fentanyl concentrations were found in 26 children to be above the minimum effective steady-state concentration needed for analgesia in adults at 10 and 34 min after intranasal administration. After the initial pharmacokinetic phase of the study, a further 265 children received intranasal fentanyl or saline during halothane or sevoflurane anesthetics. Postoperative agitation was significantly lower in the fentanyl groups with both inhalational agents, but discharge times were not different nor were parental satisfaction scores. Emesis was seen in 29–52% of children but was not different in the fentanyl-treated groups when compared to the nasal placebo group.

Finkel *et al.* (11) compared emergence after sevoflurane/N₂O/O₂ anesthesia in 150 children, aged 6 months to 5 years, who received intranasal saline, fentanyl 1 or 2 mcg·kg⁻¹, after inhalation induction. All received rectal acetaminophen 40 mg·kg⁻¹ for postoperative analgesia as well. Agitation was seen in 45% in placebo patients, 25% in fentanyl 1 mcg·kg⁻¹ group, and 15% in the fentanyl 2 mcg·kg⁻¹ group. Emesis occurred in 0% in placebo, 3.9% in fentanyl 1 mcg·kg⁻¹, and 12% in fentanyl 2 mcg·kg⁻¹ groups. Recovery and discharge times were the same in all three groups. Using intranasal fentanyl as a rescue analgesic when acetaminophen is inadequate was suggested by the investigators. Using 1 mcg·kg⁻¹ as our intranasal fentanyl dose was an attempt to keep the incidence of emesis low in our patients while affording early analgesia.

Emergence delirium scales

Watcha's 4-point agitation scale (3) was used to document the degree of agitation in our patients and the CHEOPS pain scale (4) to document pain because these were the scales that had been used by others researching this question (6,11). In 2004, Sikich and Lerman (12) described a new Pediatric Anesthesia Emergence Delirium (PAED) Scale which has been used by subsequent researchers (13,14) but unfortunately this was not available at the start of our study, being published after we had our IRB approval and had already begun recruitment. Our overall incidence of agitation (score of 3 or greater) was 13–18% with no statistical differences between the three groups. This incidence of agitation is low compared to some other studies, 14–45% in Finkel's *et al.* (11) study and 26–60% in Galinkin's *et al.* (6) study. This is perhaps because of the use of midazolam as a premedication in all of our patients. Some have reported that midazolam itself contributes to EA, but, if it does, this effect would be the same for all of our three groups.

Side effects

We did not find signs or symptoms of significant side effects caused by ketorolac or fentanyl; in particular, there were no cases of nasal irritation in the intranasal fentanyl group and only four patients (6%) with rhinorrhea. There were only four patients (6%) with bruising at the site of administration of ketorolac and no reported cases of failure to void postoperatively, which was our screening question for postoperative renal problems. Nausea

and vomiting was most common in the fentanyl group (12%) but this did not reach statistical significance in comparison with the other treatment groups.

Pain scores

We considered the rectal acetaminophen only group to be our 'placebo' group, as this is the minimal level of analgesia that we normally provide for this procedure, at our institution. Our early and late pain scores were comparable across the three groups, so providing an additional analgesic with faster onset did not improve pain scores at any stage of recovery from anesthesia. Perhaps for this reason, we also did not see any improvements in agitation scores when a second medication was used in addition to acetaminophen. As noted earlier, our results may have been favorably impacted by the standardized use of oral midazolam in all groups. A goal of our study was to determine whether EA after BM&T surgery may be exacerbated by inadequately treated pain in the immediate postoperative period and we have to conclude that it is not.

Limitations

This study has some limitations. We did not reach full accrual because of logistical reasons. However, our actual sample size was very close to the one originally calculated, and the posthoc power analysis was 86%. Also our incidence of EA was lower than previously reported. We believe this may be explained by the fact that all our patients received oral midazolam as part of the anesthetic protocol. A lower incidence of EA is a favorable outcome for all treatment groups; however, this may have made it more difficult to demonstrate differences between them. Our use of an older agitation scale, rather than the Sikich and Lerman PAED scale (12), makes it more difficult to determine whether the distress measured in our postoperative patients is owing to pain or to EA. Use of the PAED scale (12) may have better separated these two entities. What we can say is that the addition of an additional analgesic to rectal acetaminophen does not decrease distress observed in PACU in this group of patients. Bajwa *et al.* (15) compared the PAED (12), Watcha (3), and Cravero (16) scales to the observations of an experienced observer and concluded that the scales correlated well with each other, but that they all have limitations in their potential to assess whether emergence delirium (ED) is present. All patients that the trained observer diagnosed with ED also scored highly on all three of the scales. They found that the Watcha scale or the PAED scale with >12 used as the cutoff for ED had the highest overall sensitivity and specificity. Their experienced observer diagnosed ED less often than any of the scales, and this was attributed to the ability of a trained observer to recognize other forms of distress such as pain and separation anxiety because of the parents not being in PACU.

Final conclusions

What then is the ideal anesthetic for BM&T surgery? Cravero *et al.* (16) found that halothane was associated with a lower incidence of ED than sevoflurane, when used as the sole agent, with just acetaminophen for analgesia for BM&T surgery. In contrast to several previous studies (6,11,17–19), we did not find that fentanyl was effective in reducing EA, although some of these studies used a larger dose, 2.5 mcg·kg⁻¹, in others it was given iv,

not intranasally and in some cases, the procedure was a nonpainful procedure such as magnetic resonance imaging. Perhaps fentanyl has a more sedating effect when given to a patient who has no pain when compared to one who does have pain. Direct comparisons between these studies and ours are therefore difficult to make.

Our study was not originally designed to look at recovery time and discharge times as primary outcomes. To address the concern that the use of preoperative midazolam adds significantly to the total time spent at the hospital for this procedure, we compared our times in the recovery room to the times quoted for Galinkin's (6) and for Finkel's (11) studies. If we assume that processing time preoperatively and surgical time would be similar across the three hospitals and then if we add 15 min to each of our patients to allow for the administration of midazolam preoperatively, our patients' total time in the surgery center is very close to the times quoted in both Galinkin's (6) and Finkel's (11) studies.

We conclude that two-agent analgesia is not superior to acetaminophen alone for BM&T surgery when anesthetic management is with oral midazolam and sevoflurane. It did not improve postoperative pain scores, nor did it reduce the incidence of EA. The cost of a second agent and the added procedure of giving it during such a short operative procedure are not supported by our findings. Currently, a 100 mcg vial of fentanyl is \$0.26, and a single 15 mg dose of ketorolac is \$1.30. Although the cost savings for an individual case are not great, multiplied by the 1000 + cases that we do every year there is a definite cost benefit to not giving an additional medication. We conclude therefore that simple, single-agent analgesia is best for BM&T surgery in young children.

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Table 1

Patient characteristics, procedure time, and PACU times by study group

Characteristic ^a	Acetaminophen alone (<i>n</i> = 77)	Acetaminophen + fentanyl (<i>n</i> = 75)	Acetaminophen + ketorolac (<i>n</i> = 76)	<i>P</i> -value ^b
Age	1.9 (1.0)	2.2 (1.3)	2.1 (1.1)	0.13
Weight	12.8 (3.4)	13.5 (3.6)	13.3 (3.6)	0.30
Gender (% male)	62%	63%	53%	0.36
Surgery time (minutes)	13.1 (5.0)	13.4 (5.4)	12.9 (4.8)	0.90
PACU Phase I time	27.1 (14.8)	24.7 (13.5)	28.1 (14.2)	0.36
PACU Phase II time	30.4 (12.0)	36.5 (20.6)	28.2 (14.6)	0.01

^a Summary statistics shown are mean (SD), unless otherwise noted.

^b Gender distribution was compared between groups using a chi-square test. All other comparisons were conducted using Kruskal–Wallis tests. PACU, post anesthesia care unit.

Table 2

Agitation and pain scores by time point

Time point	Study group			P-value
	Acetaminophen alone (<i>n</i> = 77)	Acetaminophen + fentanyl (<i>n</i> = 75)	Acetaminophen + ketorolac (<i>n</i> = 76)	
Agitation scores				
Arousal	1.4 (0.6)	1.4 (0.6)	1.6 (0.8)	0.73
Transfer	1.5 (0.7)	1.6 (0.8)	1.5 (0.7)	0.86
Discharge	1.2 (0.6)	1.3 (0.6)	1.2 (0.5)	0.95
Pain scores				
Arousal	7.0 (1.2)	7.1 (1.4)	7.3 (1.6)	0.73
Transfer	6.8 (1.6)	7.1 (1.8)	6.7 (1.7)	0.48
Discharge	5.8 (1.7)	6.1 (1.7)	5.7 (1.6)	0.26

Summary statistics shown are mean (SD). *P*-values were computed using the Kruskal–Wallis test.

Table 3

Summaries of adverse events

Event Type	Acetaminophen alone	Acetaminophen + fentanyl	Acetaminophen + ketorolac	<i>P</i> -value
Nasal irritation or pain	1/64 ^a (2%)	0/67 ^a (0%)	1/69 ^a (1%)	<i>P</i> = 0.77 ^b
Rhinorrhea	5/64 (8%)	4/67 (6%)	10/69 (14%)	<i>P</i> = 0.20 ^c
Nausea or vomiting	4/64 (6%)	8/67 (12%)	2/69 (3%)	<i>P</i> = 0.12 ^b

^aTotal patient numbers are fewer in this table when compared to the rest of the study – not all patients could be reached for a postoperative follow-up call, and so side effects were not assessed in all patients.

^bFisher's exact test.

^cchi-square test.