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Transnasal Butorphanol Is Effective for Postoperative Pain Relief in Children Undergoing Myringotomy

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Background: **More than 70% of children require analgesics after bilateral myringotomy and tube placement (BMT). Because anesthesia for BMT is generally provided by face mask without placement of an intravenous catheter, an alternative route for analgesia administration is needed. Transnasal butorphanol is effective in relieving postoperative pain in adults and children. The effectiveness of transnasal butorphanol for postoperative pain management in children undergoing BMT was studied.**

Methods: **This double-blinded, placebo-controlled study compared the postoperative analgesic effects of transnasal butorphanol administered after the induction of anesthesia. Sixty children classified as American Society of Anesthesiologists physical status 1 or 2 who were aged 6 months or older and scheduled for elective BMT were randomized to receive transnasal placebo or 5, 15, or 25 μg/kg butorphanol. Postoperative pain was assessed using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) on arrival in the postanesthesia care unit and at 5, 10, 15, 30, 45, and 60 min.**

Results: **The CHEOP scores were significantly less in the 25 μg/kg transnasal butorphanol group compared with controls. Significantly fewer children received rescue analgesia in the 25 μg/kg transnasal butorphanol group compared with controls (n = 1 and 8, respectively; *P* = 0.02).**

Conclusions: **Transnasal butorphanol given in a dose of 25 μg/kg after induction of anesthesia provided adequate postoperative pain relief in children undergoing BMT. (Key words: Analgesia; intranasal; transmucosal.)**

DESPITE the brief duration of bilateral myringotomy and tube placement (BMT), the need for analgesia after this procedure in children is well recognized.[1,2] More than 70% of children undergoing BMT who do not receive preoperative analgesics require analgesic therapy in the early postoperative period.[2] Anesthesia for BMT is typically performed without intravenous access, so another route of analgesic administration is necessary. Transnasal butorphanol is a synthetic opioid agonist-antagonist analgesic agent recommended to relieve moderate to severe pain.[3] Butorphanol administered transnasally has been used successfully for analgesia after various surgical procedures in adults[4-6] and children.[7] This double-blinded, placebo-controlled study was designed to compare the postoperative analgesic effects of three doses of butorphanol (5, 15, or 25 μg/kg) administered transnasally after induction of anesthesia in children undergoing BMT.

Materials and Methods

Sixty healthy children aged 6 months or older and classified as American Society of Anesthesiologists physical status 1 or 2 who were scheduled to undergo elective outpatient BMT were enrolled in the study. The study was approved by the Indiana University-Purdue University Indianapolis Institutional Review Board, and written informed consent was obtained from the parents or legal guardians of each child.

No preinduction medications were administered. Anesthesia was induced and maintained with halothane, nitrous oxide, and oxygen by face mask. After induction

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of anesthesia but before beginning surgery, patients received one of four preservative-free transnasal solutions according to a randomized, double-blinded, placebo-controlled protocol. Group 1 received saline (placebo), group 2 received 5 μg/kg butorphanol, group 3 received 15 μg/kg butorphanol, and group 4 received 25 μg/kg butorphanol. The drug was prepared by a physician on the study team who was not involved in data collection for that particular patient. To ensure equal volume administration, the total volume administered was equal to the volume that would have been administered of 25 μg/kg butorphanol at that child's weight. Preservative-free saline was mixed with butorphanol in groups 2 and 3 to bring the volume to this level. The drug was administered *via* a 1-ml syringe, placing one drop at a time on the patient's nasal mucosa as they inhaled.

The child's behavior was assessed at the time of induction of anesthesia using a four-point scale where 1 = calm, quiet; 2 = crying, but can be consoled; 3 = crying, cannot be consoled; and 4 = agitated and thrashing.[2] The duration of anesthesia (time from induction of anesthesia to arrival in the postanesthesia care unit [PACU]) was recorded.

On arrival in the PACU and at 5, 10, 15, 30, 45, and 60 min, an observer, unaware of group assignment, assessed the child's pain using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) pain scale[8] (table 1). This system scores, on a scale of 4 to 13, the following areas: crying, facial expression, verbal statements, position of torso, touching of the wound, and movement of legs. To assure validity of pain and behavioral scores, assessments were made by a team of two physicians and one research assistant who were trained in this method and who had been judged on their ability to make consistent and accurate evaluations. A single observer recorded all CHEOPS scores, behavior scores, times, hemoglobin oxygen saturations, and complications. Children with oxygen saturations <95% were given supplemental oxygen and then weaned to room air as tolerated. Times from arrival in the PACU to eye opening, oral intake, "home readiness," and, when age appropriate, times to response to verbal commands and ambulation were recorded. A PACU nurse independently scored each patient according to the Aldrete postanesthesia recovery score.[9] As soon as the children were deemed stable (an Aldrete score >8), they were taken to the day surgery unit and reunited with their parents. Regardless of location, scoring continued until 60 min after arrival in the PACU. The time from arrival in the PACU to transfer to the day surgery unit was recorded. The behavior of the child before and after reunion with his or her parents was again assessed using the four-point scale as described before in which 1 = calm, quiet; 2 = crying, but can be consoled; 3 = crying, cannot be consoled; and 4 = agitated and thrashing. Patients who were deemed to be in pain (*i.e.*, they had a CHEOPS score ≥10) or who requested pain relief while in the PACU or day surgery unit received a rescue dose of 15 mg/kg oral acetaminophen. Patients were discharged home when they were awake, alert, and comfortable. The minimum stay in the day surgery unit after mask anesthetics is 1 h after admission to the PACU according to protocol, so no child was discharged home sooner than 1 h. All episodes of emesis were recorded.

Table 1. Behavioral Definitions and Scoring of CHEOPS[8]

Item	Behavior	Score
Cry	No cry	1
	Moaning	2
	Crying	2
	Scream	3
Facial	Smiling	0
	Composed	1
	Grimace	2
Child verbal	Positive	0
	None	1
	Other complaints	1
	Pain complaints	2
	Both complaints	2
Torso	Neutral	1
	Shifting	2
	Tense	2
	Shivering	2
	Upright	2
	Restrained	2
Touch	Not touching	1
	Reach	2
	Touch	2
	Grab	2
	Restrained	2
Legs	Neutral	1
	Squirming/kicking	2
	Drawn up/tensed	2
	Standing	2
	Restrained	2

Statistical Analysis

Sample size calculations based on a proportion of 0.700 in the placebo group and a proportion of 0.150 in

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Table 2. Demographic Data and Duration of Anesthesia

	Placebo	Butorphanol		
		5 μg/kg	15 μg/kg	25 μg/kg
Age (yr) (mean ± SD)	2.4 ± 2.0	3.6 ± 1.9	3.6 ± 2.2	3.8 ± 2.6
Weight (kg) (mean ± SD)	12.7 ± 6.6	16.9 ± 7.9	15.2 ± 4.6	16.6 ± 7.3
Sex (M/F)	8/7	12/3	12/3	13/2
ASA (I/II)	11/4	7/8	8/7	9/6
Median duration of anesthesia (min)	19	23	21	24

a treatment group were determined by power analysis. These sample sizes gave 80% power to detect a difference. Proportions were compared in independent samples. The test of equality of proportions was done at the 0.05 level of significance. A sample size of 15 from each group gives a probability of 0.806 of rejecting the null hypothesis of equal proportions if the alternative holds. That is, accrued sample sizes give 80% power to detect a difference in proportions of 70% compared with 15% or less.

Categorical variables were compared among treatment groups using Fisher's exact test.[10] Continuous variables were analyzed using an analysis of variance. If overall differences were detected, pairwise *t* tests were performed to compare each treatment group with the placebo group. A repeated measures analysis of variance was used to analyze group and time effects on Aldrete scores determined at 0 and 30 min.[11] To compare the effect of reunion with parents on behavior scores, the marginal homogeneity test was performed.[10]

All variables that measured the time it took for an event to happen were first analyzed using a log-rank test to identify any overall differences among the four groups.[12] For all analyses yielding a significant overall group effect, pairwise Wald chi-square tests were performed using proportional hazards regression to compare each of the treatment groups with the baseline group.

Results

Sixty patients were included in the study, with 15 children in each group. No significant group effects were found for age, weight, sex, ASA status, and median duration of anesthesia (table 2).

Figure 1 shows the probability of maintaining comfort (*i.e.*, of not requiring rescue analgesia [CHEOPS <10]) at a given time. Group 1 (placebo) had significantly shorter times to rescue than did group 4 (25 μg/kg; pairwise Wald chi-square test, $P = 0.041$). Group 1 was not significantly different from groups 2 (5 μg/kg) or 3 (15 μg/kg).

Table 3 shows recovery data. There were no significant group effects in the times from arrival in the PACU to eye opening, response to commands, ambulation, and achievement of discharge criteria for home readiness. Significant group effects were found for time to oral intake ($P = 0.030$). Group 4 had significantly longer times to oral intake than did group 1 ($P = 0.012$). Significantly fewer children in group 4 required "rescue" analgesia compared with group 1. There was no statistical difference in postoperative emesis among the four groups.

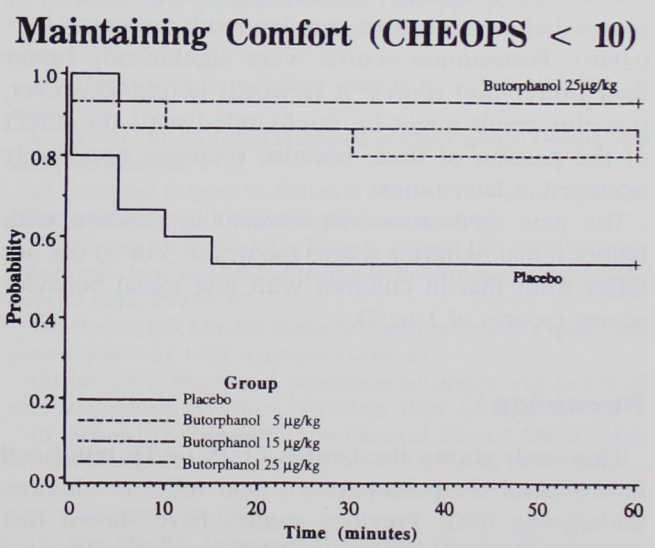

Fig. 1. Kaplan-Meier curve of the probability of remaining comfortable (*i.e.*, Children's Hospital of Eastern Ontario Pain Scale score <10) after transnasal butorphanol or placebo.

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Table 3. Recovery Data

	Placebo	Butorphanol 5 μg/kg	Butorphanol 15 μg/kg	Butorphanol 25 μg/kg
Eye opening (min)	10	10	14	18
Response to commands (min)	39	20	20	25
Oral intake (min)	27	44†	32	43†
Ambulation (min)	52	44	60	56
Discharge home (min)	62	67	65	61
Postoperative emesis (%)	7	20	33	7
"Rescue" analgesia required (%)	53	20	20	7†
O_2 saturation (%)	97 ± 1	97 ± 1	96 ± 1†	94 ± 1†
Aldrete scores				
Time 0 min	9 ± 1‡	7 ± 2	7 ± 2	7 ± 1
Time 30 min	10 ± 1	9 ± 1	9 ± 1	9 ± 1

* All times are median from arrival in the PACU.

† Significantly different from Group I.

‡ Significantly higher than Group II and IV, marginally higher than Group III.

There was a significant overall increase in Aldrete scores from 0 to 30 min. Furthermore, there was a significant overall group effect ($P = 0.005$). Specifically Aldrete scores on arrival in the PACU were significantly higher for group 1 compared with those for group 2 ($P = 0.001$) and group 4 ($P = 0.003$). There were, however, no significant group differences at 30 min.

There was a significant overall difference in behavior scores before and after reunion with parents ($P = 0.046$). Postreunion scores were significantly better than prereunion scores. It is worth noting, however, that this result might be confounded with the effect of the passing of time, because reunions necessarily occurred at later times.

The pain medication requirement in children with higher initial behavior scores (scores of 3 or 4) did not differ from that in children with low initial behavior scores (scores of 1 or 2).

Discussion

This study shows the benefit of 25 μg/kg transnasal butorphanol for postoperative pain relief in children undergoing BMT. Previous studies have shown that >70% of children undergoing BMT require analgesics.[2] Anesthesia for children undergoing BMT is typically done *via* face mask without intravenous access. Therefore, another route, such as the transnasal approach, is needed for analgesic administration.

Butorphanol is a synthetic agonist-antagonist opioid with a relatively low abuse potential.[13] It has been available in an injectable form since 1979 and in a transnasal preparation since 1992. Transnasal butorphanol is as effective as equipotent doses of intramuscular meperidine[4,5] and morphine[6] for relieving postoperative pain in adults. This convenient mode of delivering butorphanol has been used effectively in adults to treat migraine headaches[14,15] and for postoperative pain after various surgical procedures.[4,6,16–18] Tobias and Rasmussen[7] showed the utility of transnasal butorphanol in children for postoperative analgesia after orthopedic and plastic surgery.

Pain after BMT is present on awakening and gradually subsides in the ensuing 45–60 min.[1] The onset of analgesia after transnasal administration of butorphanol is within 15 min, with peak analgesic activity within 1 or 2 h in adults.[19] The mean duration of surgery in this study was approximately 20 min. Administering transnasal butorphanol immediately after induction of anesthesia gives adequate time for the analgesic effects of butorphanol to develop, making this drug ideal for postoperative analgesia after BMT. The bioavailability of butorphanol administered transnasally is 60–70%.[19] After the initial absorption–distribution phase, transnasally administered butorphanol follows similar single-dose pharmacokinetics administered intravenously or intramuscularly.[19]

Transnasally administered drugs rapidly cross the cribriform plate into the central nervous system.[20] Neurotoxicity from the drug or its preservative is a potential concern. Ketamine and midazolam applied directly to neural tissues are neurotoxic.[21] Chlorobutanol, a preservative used in some formulations of ketamine, is a source of neurotoxicity.[22] The butorphanol administered in this study was obtained from the preservative-free injectable formulation and diluted when necessary with preservative-free sodium chloride.

Pediatric pain assessment during the postoperative period is a complex task. Self-reporting pain, the gold standard for pain measurement, is not available in the immediate postoperative period in children too young to speak or who are sedated. Facial expression, vocalization, and body movement are typically associated with pain. Although inferring pain from behavior is fraught with difficulties, behavior scales have been developed to measure postoperative pain in infants and children.

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One such scoring system, CHEOPS, is a well-accepted scoring method to assess postoperative pain in children.[8] Although Beyer *et al.*[23] indicated poor correlation between self-reporting and CHEOPS in children after surgery and recommended combining behavioral measurements with self-reports, many of our children were unable to verbalize. Children (or their parents) who requested pain medication were given rescue analgesia. In preliminary work, no verbal child with a CHEOPS score <10 requested pain medication. Therefore a CHEOPS score ≥ 10 was set as the level of intervention for rescue analgesia. During this study, two children and three parents requested pain medication.

It is difficult to distinguish between pain and other causes of distress in children.[24] Fear and anxiety can enhance pain. Our results confirm those of Orobello *et al.*,[1] who showed that children agitated before induction of anesthesia for BMT do not awaken with higher levels of pain. Parents can affect a child's level of distress. This study showed improvement of behavior scores after reunion of children with their parent(s). It is important to note that we could not separate the effects of parental presence and those due to the passing of time in this study.

One of the most frequent side effects of transnasal butorphanol is sedation.[25] Aldrete scores were obtained in the PACU to assess the level of sedation. Children receiving 5 and 25 μg/kg transnasal butorphanol had significantly lower Aldrete scores, reflecting a higher level of sedation, and those receiving 15 μg/kg had marginally lower Aldrete scores on arrival in the PACU. By 30 min these differences had resolved. We believe the early sedation provided by butorphanol was advantageous because it provided a smooth recovery. Although the oxygen saturation on arrival in the PACU was statistically lower in both the 15 and 25 μg/kg groups compared with placebo (96% and 94% *vs.* 97%), this was not clinically important. All children were monitored with pulse oximetry, and oxygen was readily available and used when indicated. All children were successfully weaned to room air before discharge from the PACU. Time to oral intake was longer in the 25 μg/kg butorphanol group. Although these factors may indicate increased sedation in children receiving the higher doses of transnasal butorphanol, the time to discharge home was not delayed, so any early sedation resolved by the time of discharge 1 h after arrival in the PACU. There was no difference in the incidence of postoperative in-hospital vomiting among the groups.

In conclusion, 25 μg/kg transnasal butorphanol significantly reduced the need for rescue analgesia after BMT in children.

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