

## A Single Dose of Morphine Sulfate Increases the Incidence of Vomiting after Outpatient Inguinal Surgery in Children

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**Background:** In children, opioids are valuable both for their analgesic properties and for their salutary effect on emergence delirium. Although intraoperative administration of opioids is often cited as the cause of postoperative emesis, few data quantitating the magnitude of this effect exist.

**Methods:** Patients undergoing inguinal surgery as outpatients were randomly assigned to one of two groups. One group received a single intravenous dose of morphine 0.1 mg/kg (morphine group), and the other (control) group had the identical anesthetic but instead received saline. Intravenous ketorolac was administered in response to verbal complaints of pain or a Children's Hospital of Eastern Ontario Pain Score greater than 9 on two successive evaluations performed at 5-min intervals. The authors compared the incidence of postoperative emesis and emergence, behavior, and pain scores between the two groups.

**Results:** Patients in the morphine group ( $n = 48$ ) were  $5.6 \pm 2.8$  yr old and weighed  $20.8 \pm 7.8$  kg, and those in the control group ( $n = 49$ ) were  $4.5 \pm 2.9$  yr old and weighed  $18.9 \pm 9.2$  kg. More patients in the morphine group were cooperative and deeply asleep both on arrival and through the first 30 min of their stay in the postanesthesia care unit (PACU) ( $P < 0.05$ ). Sixty-three percent of the children in the control group

received ketorolac in the PACU compared with 20% of the morphine group ( $P < 0.01$ ). The incidence of emesis for the 24 h after arrival in the PACU was 56% for those who received morphine compared with 25% in the control group ( $P < 0.01$ ).

**Conclusions:** For children undergoing inguinal surgery, the administration of a single dose of intravenous morphine after the induction of anesthesia smooths emergence from anesthesia as assessed by improved cooperation and sedation in the PACU, decreases the need for postoperative analgesics, but increases the incidence of vomiting in the first 24 h after surgery. (Key words: Anesthesia; outpatient; pediatric. Complications: vomiting. Analgesics, opioid: morphine.)

IN a recent review, Smith recounts the numerous advances in the field of pediatric anesthesia. He also notes that "it has not been possible to gain adequate control of three of the most common and bothersome features of anesthesia met by our small patients—namely fear, discomfort and nausea."<sup>1</sup> Although substantial progress has been made in each of these areas, the prevention of postoperative nausea and vomiting remains the focus of considerable attention. For infants and children postoperative vomiting is not only uncomfortable it represents the most frequent complication of general anesthesia<sup>2</sup> and the most frequent reason for unscheduled admission after outpatient surgery.<sup>3</sup>

In children, opioids are valuable both for their analgesic properties and for their salutary effects on emergence delirium.<sup>4</sup> Although the administration of opioids is frequently cited as a cause of postoperative emesis, the magnitude of this effect has been difficult to quantify. In a previous study involving children undergoing a wide variety of outpatient operations, we found that the intraoperative administration of opioids significantly affected the incidence of postoperative vomiting.<sup>5</sup> However, when the effects of age and procedure (limited to inguinal surgery) were controlled for, no effect could be demonstrated. Patients 2–18 yr old who received intraoperative morphine as part of their anesthetic management for hernia repair, experienced a 54% incidence of vomiting in the first 24 h

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after surgery compared with 48% for those who did not receive an opioid (unpublished data from Schreiner *et al.*<sup>5</sup>). However, most patients had received meperidine as part of an oral preanesthetic medication or an opioid in the postanesthesia care unit (PACU) to treat pain. We therefore, designed a study in children undergoing inguinal surgery that controlled for these confounding variables to examine the effects of a single intravenous dose of morphine on postoperative vomiting and to document the effect of morphine on emergence excitement in the PACU.

### Materials and Methods

After approval from the institutional review board had been obtained, 97 ASA physical status 1 and 2 patients ages 1–12 yr scheduled for outpatient herniorrhaphy, hydrocelectomy, or orchiopexy were randomized in double blind fashion into two groups. One group received intravenous morphine 0.1 mg/kg after induction of anesthesia (morphine group), and the other received intravenous saline in an identical volume on a per-kilogram basis (control group). Other than this single injection of morphine the anesthetic management of the two groups was identical. All patients received an oral preanesthetic medication consisting of midazolam 0.5 mg/kg 15–45 min before arrival in the operating room. Anesthetic induction consisted of inhalation of halothane and 70% nitrous oxide in oxygen. Intravenous vecuronium 0.1 mg/kg was administered to facilitate tracheal intubation followed by intravenous administration of the study drug. After tracheal intubation all patients received an ilioinguinal or iliohypogastric nerve block or both by the anesthesiologist or the surgeon on the side or sides of the surgical incision with 1 mg/kg 0.25% bupivacaine per side. Anesthetic maintenance consisted of halothane in 70% nitrous oxide, balance oxygen with controlled ventilation. The anesthesiologist was given no specific instructions regarding the adjustment of the inspired halothane concentration. At the conclusion of the surgical procedure, all patients received pharmacologic antagonism of residual neuromuscular blockade with neostigmine (0.07 mg/kg) and atropine (0.02 mg/kg), underwent tracheal extubation in the operating room after resumption of spontaneous ventilation, awareness, and adequate strength, and were then transported to the PACU.

The time interval from the end of surgery until tracheal extubation, and the time of PACU admission,

PACU discharge, day surgery unit (DSU) admission, and DSU discharge were recorded. During the conduct of the study the minimum PACU and DSU stays were 60 min each. On arrival in the PACU and 10, 20, and 30 min after arrival, the following were recorded by a single observer unaware of the patient's group assignment: an emergence score (1 = awake; 2 = drowsy; 3 = asleep; and 4 = deeply asleep [difficult to arouse]), a behavior score (1 = cooperative; 2 = agitated or crying; and 3 = thrashing or requiring restraint), and a postoperative assessment of pain on the Children's Hospital of Eastern Ontario Pain Score (CHEOPS) scale.<sup>6</sup> A final set of observations was made before PACU discharge. Patients who verbalized complaints of pain or who had a CHEOPS greater than 9 in two consecutive 5-min periods received intravenous ketorolac 0.5 mg/kg (maximum dose, 1.0 mg/kg). The number of episodes of emesis was recorded by the observer in the PACU and in the DSU and the parents were contacted by telephone by a blinded observer to ascertain the frequency of vomiting from the time of hospital discharge until 24 h postoperatively. For the purposes of this study, severe vomiting was defined as five or more separate episodes of emesis. The parents were also asked if analgesics other than acetaminophen or ibuprofen had been administered to treat their child's postoperative pain.

From our previous data we estimated that the total incidence of vomiting (hospital and home) would be 54% in children who received an opioid intraoperatively.<sup>5</sup> A 25% reduction in the total incidence of vomiting was selected to represent the minimum clinically important effect. We calculated that a sample size of 198 patients in each group would be necessary to achieve an 80% power of detecting a 25% difference in the total incidence of vomiting. If a 50% reduction in the total incidence of vomiting represented the magnitude of the difference between treatments, then only 50 patients in each group would be necessary to achieve a power of 80%. We planned to analyze the data after entering approximately 100 patients to determine if the study could be terminated at that point.

Student's *t* test was used to compare differences between means of continuous variables. Ordinal data (CHEOPS, behavior score, and emergence score) was analyzed with the Mann–Whitney *U* test. Bonferroni correction was applied where appropriate to correct for multiple comparisons made over time. Contingency table analysis with Yate's correction and Fisher's exact test were used for nominal data. A  $P < 0.05$  was considered statistically significant.

## Results

Complete evaluations were collected for 96 patients: 48 in each group. Postdischarge follow-up was not possible for one patient in the morphine group, but the remainder of the data for this patient was complete. There were no differences in the demographics of the two groups (table 1). Although the duration of the surgical procedure was the same in both groups, patients who received morphine required an additional 3.5 min from the end of surgery until tracheal extubation (table 1). Both the duration of PACU stay and DSU stay averaged 10 min or less beyond the required minimum for each location (not significantly different).

On arrival in the PACU and at 10 and 30 min after arrival, more patients in the morphine group were cooperative than those in the control group (fig. 1). More children in the morphine group were deeply asleep on arrival in the PACU and for the next three evaluations (fig. 2). At the time of discharge from the PACU the behavior and emergence scores of the two groups were indistinguishable.

Patients in the control group had significantly higher CHEOPS at the time of arrival in the PACU and for the next 30 min. In the PACU, 30 patients (62.5%) in the control group exceeded the CHEOPS threshold of 9 or complained of pain and therefore received ketorolac compared with only 10 patients (20.4%) in the morphine group ( $P < 0.01$ ). At the time of discharge the difference between the groups was no longer evident and there were no differences between the groups in their requirements for analgesics in the DSU (table 2). Of the patients who required ketorolac in either the PACU or DSU, only 3 (14%) of 21 of the morphine group required two doses, compared with 20 (56%) of 35 of the control group. At home, 5 patients in the

Table 1. Demographic Data

	Morphine		Control	P
	N	49	48	...
Age (yr ± SD)		5.6 ± 2.8	4.5 ± 2.9	.053
Weight (kg ± SD)		20.8 ± 7.8	18.9 ± 9.2	0.29
Gender M/F		34/15	40/8	0.17
Block by surgeon (%)		39%	33%	0.67
Surgical time (min ± SD)	42	± 24	45 ± 21	0.59
End surgery to tracheal extubation (min ± SD)		9.7 ± 6	6.2 ± 4	<0.01
Duration PACU stay	65	± 12	66 ± 21	0.73
Duration DSU stay	70	± 17	67 ± 19	0.41

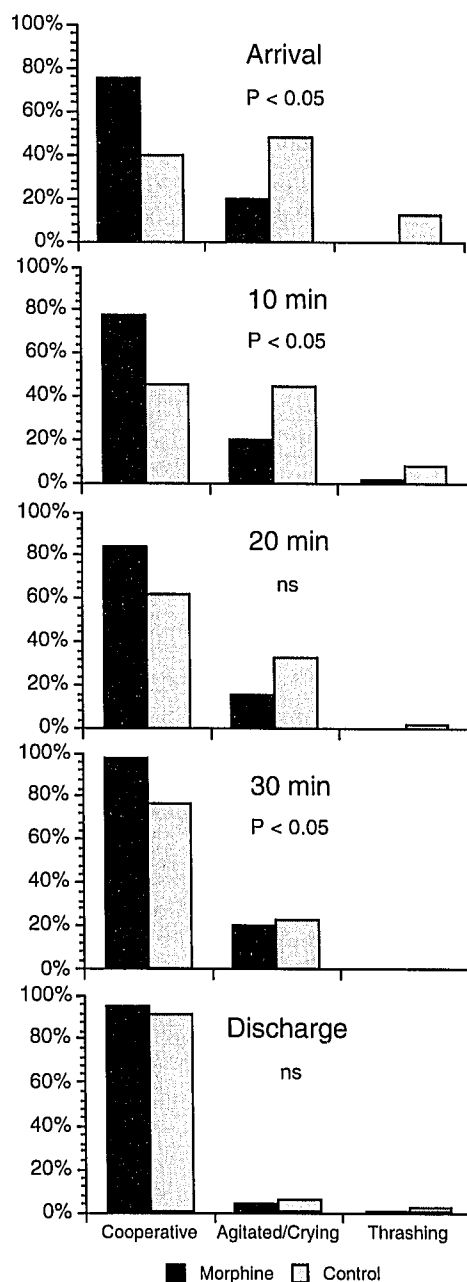


Fig. 1. The distribution of behavior scores for the two groups are shown on arrival to the postanesthesia care unit (PACU); 10, 20, and 30 min after arrival; and at discharge from the PACU. More patients who received morphine in the operating room were cooperative and less were likely to thrash and require active restraint at the time of arrival in the PACU, 10 min after arrival, and 30 min later ( $P < 0.05$ ). At the time of discharge from the PACU there were no differences in the two groups.

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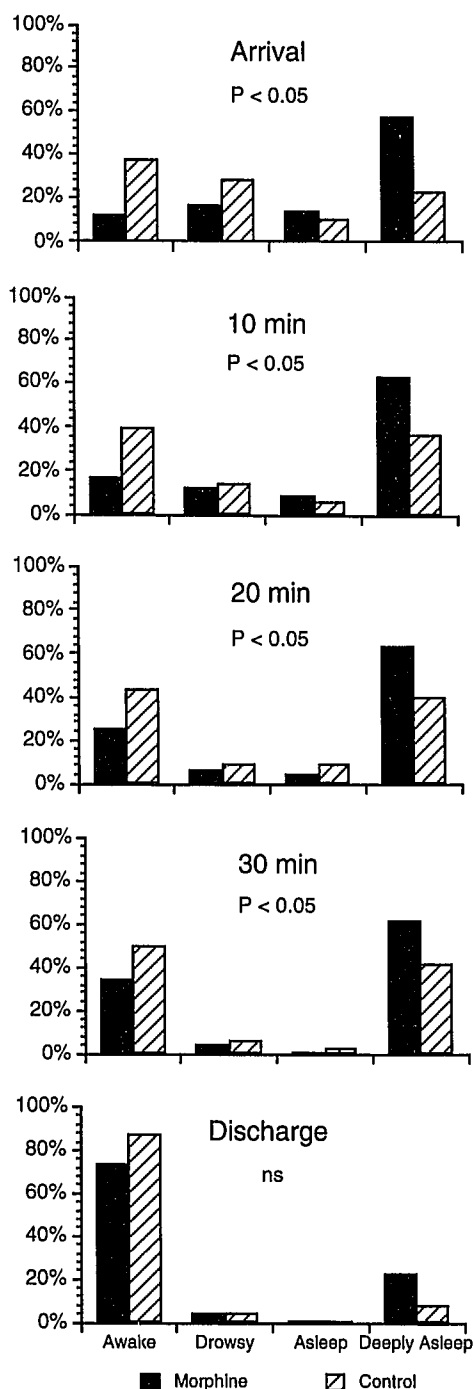


Fig. 2. The distribution of emergence scores for the two groups at the time of arrival in the postanesthesia care unit (PACU); 10, 20, and 30 min after arrival; and at discharge from the PACU. For the first 30 min significantly more patients from the morphine group were asleep or deeply asleep than patients from the control group ( $P < 0.05$ ), but at PACU discharge no significant differences persisted.

morphine group and 1 in the control group received one or more doses of acetaminophen with codeine; the remainder of the patients received only acetaminophen or ibuprofen.

Postoperative vomiting was more common in patients who received morphine compared with those who received placebo (table 2). The 95% confidence interval for the difference of 31% in the incidence of vomiting for the two groups (56% vs. 25%) ranged from 12% to 50%. Nine (19%) children from the morphine group had five or more episodes of emesis, compared with only two (4%) children in the control group; the 95% confidence interval for the 15% difference in the incidence of severe vomiting ranged from 2% to 27%. Of the patients with emesis in the first 24 h after surgery, 37% of morphine group patients vomited for the first time after discharge compared with only 17% of control group patients.

The difference in the ages of the two groups raised the possibility that part of the decreased incidence of vomiting in the placebo group could be attributed to an age effect. Twenty-eight children in the study, 8 in the morphine group and 20 in the control group, were less than 3 yr of age. However, even with these 28 patients excluded from the analysis the total incidence of vomiting in the remainder of the morphine group was 63% compared with 31% for the control group ( $P = 0.015$ ).

To examine a possible deleterious effect of ketorolac on postoperative emesis, control group patients were divided into those who received and those who did not receive ketorolac. Of the 48 patients in the control group, 35 received ketorolac, and 5 (14%) vomited in the first 24 h after surgery. The remaining 13 control patients were assessed to have adequate pain control

Table 2. Number and Percentage of Patients Receiving Ketorolac and Vomiting by Location

	Morphine		Control	P
	N	49	48	
Ketorolac Rescue				
PACU (%)	10	(20.4)	30 (62.5)	<0.01
DSU (%)	11	(22.4)	7 (14.5)	0.46
PACU ± DSU (%)	21	(42.9)	35 (72.9)	<0.01
Vomiting				
Hospital [PACU ± DSU] (%)	17	(34.7)	10 (20.8)	.19
N at follow-up	48		48	
Home [24 hrs post discharge] (%)	24	(50)	8 (16.7)	<0.01
Total [Hospital + Home] (%)	27	(56.3)	12 (25)	<0.01

without a need for a systemic analgesic while in the hospital. Seven (54%) of the 13 experienced one or more episodes of vomiting before or after discharge from the hospital.

## Discussion

A number of variables have been shown to correlate with vomiting after outpatient surgery in children, including the type of surgical procedure, the age of the child, mandatory resumption of ingestion of oral liquids and administration of opioids. Our data demonstrate that patients who received a single intravenous dose of 0.1 mg/kg morphine to supplement a regional nerve block had more than double the incidence of postoperative vomiting in the first 24 h after surgery compared with patients who received a regional nerve block with or without rescue therapy with ketorolac. Confounding variables were controlled by avoiding all opioids with the exception of the single dose administered to the morphine group in the operating room. Oral midazolam was used as a preanesthetic medication, intravenous ketorolac was used for a rescue analgesic for postoperative pain, and only patients undergoing inguinal surgery were eligible for entry into the study. The control group was slightly younger than the morphine group, but even when all patients less than 3 yr of age were excluded from analysis, the remainder of the morphine group still had double the incidence of vomiting of those in the control group.

Many studies have implicated opioids as a causative factor for increased postoperative nausea and vomiting. In larger doses opioids stimulate the chemoreceptor trigger zone and the vestibular apparatus. In smaller doses, opioids may stimulate an anatomically distinct antiemetic center.<sup>7,8</sup> The high incidence of vomiting in the morphine group after discharge from the hospital may be attributable to morphine's effect on the vestibular apparatus associated with the increase in activity level as recovery progresses.<sup>9</sup> A dose-related effect on postoperative vomiting has been described for sufentanil and it is possible that a similar effect might occur with other opioids.<sup>10</sup> Although it is possible that a different opioid would have significantly reduced or increased the incidence of postoperative emesis this appears to be unlikely.<sup>11,12</sup> An approach that avoids opioids altogether is more likely to minimize postoperative emesis.

Although, morphine administration delayed the time to extubation by 3.5 min in our patients it is possible

that this was in part an artifact of the study design. We did not specifically request the clinicians to attempt to minimize the inspired concentration of halothane throughout the anesthetic. It is possible that clinicians maintained a higher level of halothane during the anesthetic because of their uncertainty about whether or not morphine had been administered. In adult patients, Gross and Alexander reported that 0.1 mg/kg morphine had no effect on MAC-awake after isoflurane anesthesia.<sup>13</sup> Despite the delay in the time to extubation, morphine clearly had beneficial effects in the immediate postoperative period. For the first 20–30 min, children in the morphine group were sleepier, calmer, required less restraint and received postoperative analgesics less often.

As others have noted, the CHEOPS proved an imperfect instrument for assessing the severity of postoperative pain after inguinal surgery.<sup>14</sup> Behavioral elements make up much of the score and children who experience emergence delirium thrash and cry. These behaviors result in a high CHEOPS and in increased administration of analgesics.<sup>15</sup> Children who received morphine were sleepier and calmer because of superior analgesia or greater sedation. Older children who were in pain often had very low CHEOPS because movement increased their discomfort. Only by interviewing these patients was the magnitude of their pain apparent. Our inability to discriminate discomfort from emergence and behavioral issues in young children resulted in a relatively high percentage of both groups receiving analgesics in the postoperative period despite receiving a regional nerve block. Failure to achieve total pain relief with one modality should not be viewed simply as failure of the technique; superior long term effects may be achieved for all patients with combinations of regional anesthetics with systemic analgesics.<sup>16</sup>

The high incidence of vomiting at home in control group patients who did not receive postoperative analgesics in the hospital may be related to underdiagnosed postoperative pain or pain that was poorly controlled after the regional nerve block wore off.<sup>17</sup> Patients who have total relief of pain after a regional anesthetic may benefit from a systemic analgesic administered while they are still comfortable for prevention of rebound pain after dissipation of the analgesia from the block.<sup>18</sup>

In conclusion, more patients who received placebo were wide awake in the PACU, experienced emergence excitement, and required supplemental ketorolac for analgesia than patients who had received morphine.

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However, by the time of discharge from the PACU, the two groups were indistinguishable. After discharge from the PACU, 0.1 mg/kg morphine substantially increased the incidence of vomiting after inguinal surgery when compared with placebo. Avoidance of opioids can play an important role in the prevention and management of postoperative vomiting provided alternative means of obtaining effective analgesia are successful.

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