

Recurrent Hypoxemia in Young Children with Obstructive Sleep Apnea Is Associated with Reduced Opioid Requirement for Analgesia

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Background: **Obstructive sleep apnea (OSA) in children is often associated with recurrent hypoxemia during sleep. In developing animals, central opioid neuropeptide content is high, and opioid receptors are up-regulated after recurrent hypoxia. The authors hypothesized that children with recurrent hypoxemia due to OSA might have altered central opioid functionality that could affect their responsiveness to opioid drugs. Using a retrospective database, we assessed the relation of age and preoperative oxygen saturation to the cumulative postoperative morphine dose administered for analgesia in children with OSA undergoing adenotonsillectomy.**

Methods: **Inclusion criteria were (1) adenotonsillectomy for OSA; (2) no concomitant pathology; (3) intraoperative administration of short-acting opioid drugs; (4) endotracheal extubation on awakening in the operating room; and (5) morphine as the parenteral, postoperative analgesic.**

Results: **Forty-six children (16 girls) fulfilled the inclusion criteria. Age and preoperative arterial oxygen saturation (Sao_2) nadir, either individually ($P = 0.023$, $P = 0.0003$, respectively) or in combination ($P = 0.00009$), exhibited a significant correlation to the morphine dose required for analgesia. Four of these children, aged 26.5 ± 13.2 months, with a preoperative Sao_2 nadir of 70.3 ± 12.9%, did not require any postoperative morphine for analgesia at all.**

Conclusions: **The authors speculate that the reduced morphine requirement for analgesia in children displaying oxygen desaturation associated with severe OSA may be related to their young age and to an up-regulation of central opioid receptors consequent to recurrent hypoxemia. In evaluating OSA in children, preoperative determination of the Sao_2 nadir is important for predicting the postoperative opioid dosage required for analgesia.**

ADENOTONSILLECTOMY is a commonly performed surgical procedure for obstructive sleep apnea (OSA) in children. Such OSA is often associated with recurrent hypoxemia during sleep.[1–5] Postoperative management includes analgesia, and morphine remains a commonly prescribed parenteral analgesic drug.

Several studies have described respiratory morbidity expressed by oxygen desaturation after adenotonsillectomy for OSA.[5–7] Although the clinical impression has been that such desaturation is more frequently observed in those children who are given morphine, to date, no correlation between these variables has been found.[5] Recently, we have reported that respiratory difficulties occurred with accepted morphine dosage and decreased within the time frame of morphine action.[8] This suggests an increased sensitivity to morphine in children with a history of OSA, for which no mechanism has so far been proposed.

In developing animals, exposure to recurrent intermittent hypoxia, such as occurs with OSA, increases the number of μ-opioid receptors in the brainstem.[9] Such a mechanism might enhance central opioid functionality.

We have therefore hypothesized that children with recurrent hypoxemia due to OSA might have an altered central opioid function that could affect their responsiveness to opioid drugs such as morphine. To test this hypothesis, we have correlated the age and preoperative oxygen saturation in children with OSA who underwent adenotonsillectomy to the cumulative postoperative dose of morphine required for analgesia, using a retrospective database in accordance with strictly defined inclusion and exclusion criteria.

Materials and Methods

This study included children with documented OSA who underwent adenotonsillectomy. The children were selected from a 2001–2002 retrospective database comprising comprehensive information pertaining to the preoperative assessment and to the intraoperative and postoperative management for each child. The study received institutional approval and did not require informed consent.

Preoperative Evaluation

The preoperative evaluation to establish the diagnosis of OSA required a history consistent with OSA and (1) an abnormal preoperative sleep study defined as an obstructive apnea/hypopnea index greater than 1 event/h; and/or (2) an abnormal overnight oximetry study documenting at least three clusters of desaturation less than 92%.[1,8] Three tests, the details of which have been reported,[5,10–13] were used to establish this diagnosis: (1)

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polysomnography, performed in the sleep laboratory; (2) a cardiorespiratory sleep study performed in the child's home; and/or (3) overnight oximetry, performed in the hospital or in the child's home. Of the many variables recorded, the current work focuses on the nadir oxygen saturation (Sa_{O_2} nadir). The Sa_{O_2} nadir was validated by visual inspection of a computerized data record and was defined as the minimal hemoglobin oxygen saturation, regardless of its duration. A validated Sa_{O_2} nadir was also determined from the event graphs obtained from oximetry studies.[11,14]

Anesthetic Management

Children were included in this study if they had no pathology other than OSA. No child was premedicated. All children had general anesthesia for their adenotonsillectomy, tracheal intubation with assisted ventilation, short-acting opioids during the induction of anesthesia, nitrous oxide with isoflurane or sevoflurane throughout anesthesia, tracheal extubation on awakening from anesthesia in the operating room, and the use of morphine as the parenteral, postoperative analgesic. The intravenous opioid administered during surgery was fentanyl or sufentanil (duration of action $\approx$ 30 min[15]). The doses of these drugs were expressed as morphine equivalents, such that 0.001 mg fentanyl and 0.0001 mg sufentanil were equipotent to 0.1 mg morphine.[15] Adjunct medications given intraoperatively that may have influenced postoperative morphine dosing included acetaminophen, ketorolac, ketamine, and dexamethasone.[16–19] Postoperative pain was treated in accordance with a physician-prescribed morphine dose, which was repeated at 10-min intervals resulting in a cumulative postoperative morphine dose necessary to achieve a Children's Hospital of Eastern Ontario Pain Score of 6 (*i.e.*, cessation of crying, moaning, grimacing, restlessness, and verbal reports of pain) or subjective comfort (denying pain).[20]

Statistical Analysis

The anthropomorphic characteristics of the patients and all other data were described as mean ± SD. The normality of the distribution of each variable was tested with the Shapiro-Wilk W test. The potential effect of the adjunct medications in their various combinations on the morphine dose was tested with one-way analysis of variance. The potential influence of the intraoperative morphine equivalent on the cumulative postoperative morphine dose was tested using regression analysis.

The relation of the predictor variables, namely, age, preoperative Sa_{O_2} nadir, intraoperative morphine equivalent, acetaminophen, ketorolac, ketamine, and dexamethasone, to the morphine dose was examined by multiple regression as well as a backward stepwise multiple regression procedure (Statistica, version 6; StatSoft, Inc., Tulsa, OK). Age, preoperative Sa_{O_2} nadir, intraoperative morphine equivalents, and the cumulative postoperative morphine dose were treated as continuous variables. The adjunct drugs acetaminophen, ketorolac, and ketamine were treated as categorical variables (in which 1 denoted that the drug had been given and 0 denoted that it had not) because they were administered at fixed doses and not all patients received all drugs. The dose of the adjunct drug dexamethasone was treated as a continuous variable. Significance was defined at $P < 0.05$ throughout.

Table 1. Patients (n = 46, 16 Girls), Surgery, and Drug Dosing Characteristics

Variable	Mean ± SD	n
Age, months	43.3 ± 18.6	46
Weight, kg	16.3 ± 4.7	46
Preoperative Sa_{O_2} nadir, %	83.0 ± 9.7	46
Preoperative apnea/hypopnea index, events/h	12.8 ± 9.3	21
Surgery time of day, h	10:13 ± 2.3	46
Duration of surgery, min	40.7 ± 10.2	46
Intraoperative morphine equivalents, mg/kg intravenous	0.16 ± 0.09	46
Intraoperative acetaminophen, mg/kg p.r.	36.0 ± 6.5	42
Intraoperative ketorolac, mg/kg intravenous	0.64 ± 0.42	6
Intraoperative ketamine, mg/kg intravenous	0.16 ± 0.05	12
Intraoperative dexamethasone, mg/kg intravenous	0.32 ± 0.15	25
Postoperative morphine, mg/kg intravenous	0.09 ± 0.04	42
End-anesthesia to morphine analgesia interval, min	16.9 ± 25.0	42

p.r. = per rectum; Sa_{O_2} = arterial oxygen saturation.

Results

Forty-six (16 girls) out of the 102 consecutive children who underwent adenotonsillectomy between November 2001 and December 2002 met the inclusion criteria set for the current study. The diagnosis of OSA was made by oximetry alone (n = 25), by a combination of oximetry and sleep studies (n = 17), or, in those children who displayed near normal oxygen saturation, from the apnea/hypopnea index (8.0 ± 6.0 events/h; n = 4).

The anthropomorphic characteristics of the children included in this study as well as data related to their surgery, the intraoperative fentanyl (n = 34) or sufentanil (n = 12) regimen (expressed as morphine equivalents), the adjunct medication regimen, and cumulative postoperative morphine dosing are presented in table 1. Age and the apnea/hypopnea index were the only variables that displayed a normal distribution. The adjunct medications used intraoperatively in various combinations did not influence the corresponding morphine doses required for analgesia (table 2). There was no

Table 2. Adjunct Medication Combinations and the Corresponding Cumulative Postoperative Morphine Doses

Adjunct Medication Combination	Morphine Dose (Mean ± SD), mg/kg	n
Acetaminophen	0.10 ± 0.04	18
Acetaminophen, dexamethasone, and ketamine	0.08 ± 0.03	10
Acetaminophen and dexamethasone	0.08 ± 0.04	9
Acetaminophen, dexamethasone, and ketoralac	0.12 ± 0.04	3
Nil	0.02 ± 0.03	2
Acetaminophen and ketorolac	0.08	1
Dexamethasone and ketamine	0.09	1
Dexamethasone and ketorolac	0.04	1
Acetaminophen, dexamethasone, ketoralac, and ketamine	0	1

One-way analysis of variance revealed no influence of the adjunct medication combinations on the cumulative postoperative morphine dosage ($F_{3,36}$ = 1.782, P = 0.168). The number of the patients included in the analysis of variance was 40 instead of the total 46 because the group receiving no adjunct medications (2 children) and the groups with n = 1 (4 children) were excluded from the analysis.

correlation between age or preoperative Sao_2 nadir and either the intraoperative opioid or the physician-prescribed morphine dose. There was no correlation between the administered intraoperative opioid dose and the physician-prescribed morphine dose (0.05 ± 0.02 mg/kg). In addition, there was no correlation between the administered intraoperative opioid and the cumulative postoperative morphine dose (fig. 1).

There was no significant correlation among the predictor variables. Multiple regression indicated an overall significant relation between the seven predictor variables and the cumulative postoperative morphine dose

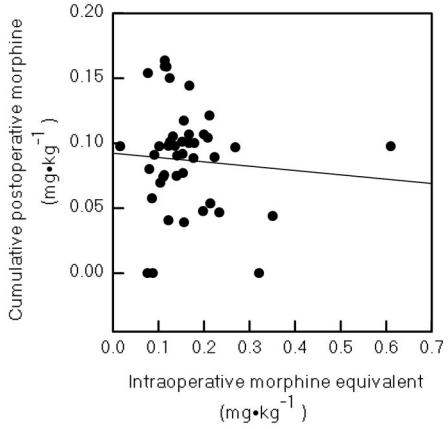

Fig. 1. Intraoperative opioid (in morphine equivalents) does not correlate with the cumulative postoperative morphine dose. The regression between the two variables is defined by the following equation:

Cumulative Postoperative Morphine =

−0.0335 · Intraoperative Morphine Equivalent + 0.092.

***R* = 0.0759; R^2 = 0.0058; *P* = 0.616.**

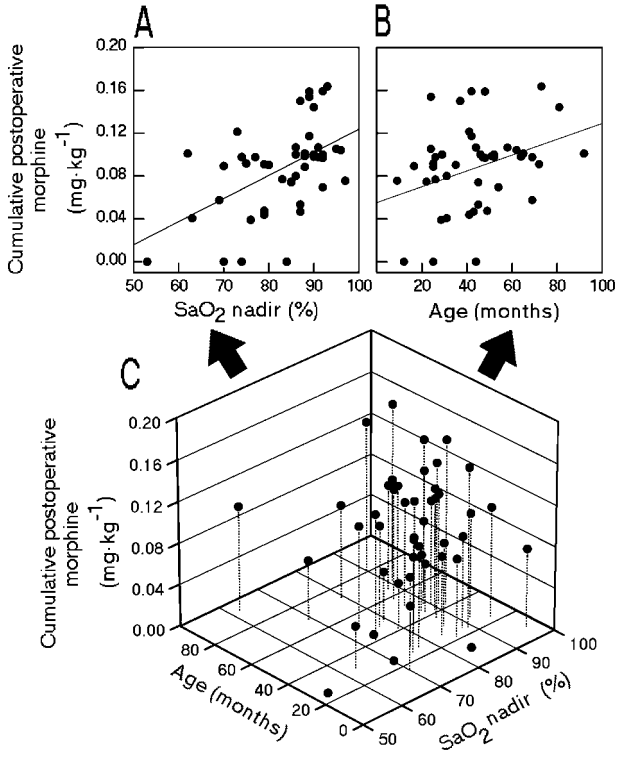

Fig. 2. Age (months) and preoperative arterial oxygen saturation (Sao_2) nadir (%) are significantly correlated with the cumulative postoperative morphine dose (mg/kg) required for analgesia after adenotonsillectomy. The correlation of each variable with the cumulative postoperative morphine dose is shown in the two-dimensional plots (*A* and *B*), and the correlation of the combined variables with the cumulative postoperative morphine dose is shown in a three-dimensional scatter plot (*C*). Estimates for each child are depicted with a *filled circle*. The magnitude of the cumulative postoperative morphine dose in the three-dimensional scatter plot is depicted by the height of the stem supporting each circle. The less than 46 observed points are due to superimposed data. The regression describing the relation among the three variables is defined by the following equation:

Cumulative Postoperative Morphine (mg/kg)

= 0.0007 · Age (months) + 0.0021 · Sao_2 Nadir (%) −0.1138.

For statistical details, please consult the text.

required for analgesia ($F_{7,38}$ = 4.313, P = 0.001; R^2 = 0.443). Using partial correlations within the multiple regression analysis, this significant relation was not accounted for by either the adjunct medications or the intraoperative opioid regimen. By contrast, age and preoperative Sao_2 nadir exhibited a significant correlation to the cumulative postoperative morphine dose (r^2 = 0.083, P = 0.044; r^2 = 0.154, P = 0.001, respectively). A backward stepwise deletion of each predictor variable within the multiple regression procedure retained the significant correlation of age and preoperative Sao_2 nadir, either individually (r^2 = 0.112, P = 0.023; r^2 = 0.261, P = 0.0003, respectively) or in combination (r^2 = 0.352, $F_{2,43}$ = 11.670, P = 0.00009), with the cumulative postoperative morphine dose (fig. 2). The regression

Table 3. Details of Four Children Who Did Not Require Postoperative Morphine for Analgesia

Patient	Age, months	Sa_{O_2} Nadir, %	Intraoperative Opioid Drug	Morphine Equivalent Dose, mg/kg	Adjunct Medication	Postoperative Course
1	25	55	Fentanyl	0.32	Nil	No pain, drowsy
2	25	70	Fentanyl	0.08	Acetaminophen	No pain
3	44	74	Sufentanil	0.08	Acetaminophen Ketorolac Ketamine Dexamethasone	No pain Desaturation
4	12	84	Fentanyl	0.09	Acetaminophen Dexamethasone	No pain

Sa_{O_2} = arterial oxygen saturation.

describing the relation among the three variables is defined by the following equation:

$$\text{Cumulative Postoperative Morphine (mg/kg)} = 0.0007 \cdot \text{Age (months)} + 0.0021 \cdot Sa_{O_2}\text{ nadir (\%)} - 0.1138$$

(Standard Error of Estimate = 0.342).

From figure 2, it is evident that young age and low preoperative oxygen saturation were associated with a lower required cumulative postoperative morphine dose. Included in this figure are four children, detailed in table 3, whose age was 26.5 ± 13.2 months and preoperative Sa_{O_2} nadir was 70.3 ± 12.9%, who did not require any postoperative morphine for analgesia.

Discussion

The specific question that we have attempted to answer in the current work has been whether recurrent hypoxemia, such as occurs in OSA,[1–5] alters sensitivity to opioid analgesics. Because of the nature of this question, we adhered to strict criteria in the selection of the patient population. First, we eliminated all patients who had concomitant disease, including asthma. Second, in striving to study a homogeneous patient population, we restricted our analysis to those who underwent adenotonsillectomy. Third, we limited our patient population at surgery to those who had received short-acting opioids on induction of anesthesia. It is because of these strict inclusion criteria that the number of children included in this study was reduced from the total of 102 consecutive patients to 46.

The lack of morphine-sparing effects usually attributed to the adjunct medications[16–19] may be explained by the following considerations: (1) ketorolac and ketamine were given only to a minority of the children; (2) dexamethasone was used at a lower dose than that reported to have a morphine-sparing effect[19]; and (3) the narrow dose range of acetaminophen administered to the majority of the children precluded the demonstration of a morphine-sparing effect.

There was no evidence that a child's age or the severity of oxygen desaturation biased the intraoperative opioid regimen, nor was there any evidence for bias in the physicians' prescription or in the nurses' administration of postoperative morphine.

The lack of correlation between the short-acting opioids used intraoperatively and the cumulative postoperative morphine dose (fig. 1) can be explained by the brief duration of action of fentanyl and sufentanil[15,21] and by the time interval between their intraoperative administration and the postoperative requirement for analgesia (table 1).

The striking finding of this study, that the cumulative postoperative dose of morphine required for analgesia was significantly correlated to both the child's age and preoperative oxygen saturation, has led us to propose that these variables might be associated in some causal and mechanistic fashion. Whereas, obviously, it is impossible at this point to report molecular brain mechanisms in these children, an analogy with findings in animal models may be useful. Before such an analogy is made, however, the appropriateness of the animal model must be established. From this point of view, postnatal swine seem to be optimal models because their stage of brain development at birth seems to simulate that in full-term infants,[22] and their postnatal maturation in autonomic functions, such as sleep–wake and respiratory and cardiovascular behaviors, follows patterns similar to those in infants and children, albeit on a shortened time scale.[23,24]

In the chronically instrumented and unsedated piglet model, recurrent daily exposure to intermittent hypoxia has been shown to increase the binding of a specific agonist to μ-opioid receptors in several brainstem regions.[9] Such increased binding can be caused either by an increased affinity between the agonist and the receptor that might prolong the association between the two or by an increase in the number of receptors. Because there was no change in receptor affinity,[9] this increase in binding density can be attributed to an increase in the number of membrane-bound μ-opioid receptors. Such an increase may reduce the dose of an exogenous opioid required to accomplish a specific physiologic effect. Whereas in the above-mentioned study only respiratory-

related μ-opioid receptors were studied, it is not unreasonable to suggest that pain-related μ-opioid receptors might behave in a similar fashion. Therefore, a hypoxia-induced increased number of pain-related μ-opioid receptors in children with severe OSA might explain a heightened sensitivity to postoperative morphine given for analgesia.

The correlation between age and cumulative postoperative morphine dosage cannot be explained by an age-related change in the density of μ-opioid receptors because these do not increase over the age range studied either in pigs or in humans.[25,26] This correlation may be explained, however, by the ontogeny of opioid neuropeptides in the brain. In the same piglet model, we have shown in respiratory-related brain regions that the content of the opioid peptide β endorphin, which displays a preferred μ-opioid activity, and methionine-enkephalin, with both μ- and δ-opioid activity, is highest at birth, decreasing with postnatal age.[27] By extending the analogy of neuropeptide ontogeny to the current study and assuming similar ontogeny in pain-related brain regions, it is attractive to speculate that a higher level of endogenous ligands might reduce the amount of exogenous agonist required for a given physiologic effect. In extending this rationale to the current study, a relatively higher endogenous μ-opioid content in the younger children might have contributed to the lower required morphine dose independently of preoperative oxygen saturation.

The clinical relevance of our findings lies in the high incidence of respiratory complications reported in children with severe OSA after postoperative morphine administration.[8] Whereas the underlying mechanism of such complications is as yet unknown, it seems reasonable to speculate that at least some of those were related to the postoperative opioid regimen. If opioid requirement is lowered by youth and oxygen desaturation, as our study has shown, a normally recommended morphine dose for analgesia may be excessive for young children with severe OSA, thus producing respiratory depression. Whereas the current study lacks sufficient power to reliably report on the relation between age, preoperative oxygen desaturation, morphine dosing, and postoperative respiratory complications, a prospective study on such a relation is under way. The findings of the current study emphasize the importance of preoperative testing for oxygen desaturation in children with OSA to identify a subpopulation of children who have an increased sensitivity to opioid drugs.

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