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Recurrent Hypoxemia in Children Is Associated with Increased Analgesic Sensitivity to Opiates

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Background: **Postsurgical administration of opiates in patients with obstructive sleep apnea (OSA) has recently been linked to an increased risk for respiratory complications. The authors have attributed this association to an effect of recurrent oxygen desaturation accompanying OSA on endogenous opioid mechanisms that, in turn, alter responsiveness to subsequent administration of exogenous opiates. In a retrospective study, the authors have shown that oxygen desaturation and young age in children with OSA are correlated with a reduced opiate requirement for postoperative analgesia.**

Methods: **The current study was designed to test that conclusion prospectively in 22 children with OSA scheduled to undergo adenotonsillectomy. The children were stratified to those having displayed < 85% or ≥ 85% oxygen saturation nadir during sleep preoperatively. Using a blinded design, the children were given morphine postoperatively to achieve an identical behavioral pain score.**

Results: **As compared with children in the ≥ 85% group, the < 85% oxygen saturation nadir group required one half the total analgesic morphine dose postoperatively, indicating heightened analgesic sensitivity to morphine after recurrent hypoxemia.**

Conclusions: **Previous recurrent hypoxemia in OSA is associated with increased analgesic sensitivity to subsequent morphine administration. Therefore, opiate dosing in children with OSA must take into account a history of recurrent hypoxemia.**

ADENOTONSILLECTOMY is a common surgical procedure in pediatrics and is indicated for the treatment of obstructive sleep apnea (OSA) caused by enlarged adenoids and/or tonsils. Postsurgical administration of opiates in patients with OSA has recently been linked to an increased risk for respiratory complications.[1] We reported that the onset of postadenotonsillectomy respiratory complications in children with OSA began within 2 h of morphine administration.[2] We have attributed the association between the OSA and the postsurgical respiratory complications to an effect of recurrent oxygen desaturation accompanying OSA on endogenous opioid mechanisms that, in turn, alter responsiveness to exogenous opiates.[3] This association is supported by studies showing that it was the preoperative oxygen desaturation that presaged the postsurgical respiratory complications, including respiratory depression, in both adults and children with OSA.[4–7]

In a recent retrospective study, we have shown in children with OSA the existence of a correlation between oxygen desaturation during sleep and age on the one hand and total opiate requirement for postoperative analgesia on the other, in which a low oxygen saturation nadir and young age were associated with a reduced total analgesic morphine dose.[3] Multiple linear regression yielded an equation describing the characteristics of that correlation. From that equation, the total analgesic morphine dose required postsurgically for each child with OSA undergoing adenotonsillectomy can be calculated based on the child's preoperative oxygen saturation nadir and age.[3]

The current study was designed to test the conclusions from the retrospective study using a prospective, blinded design in children diagnosed with OSA and scheduled to undergo adenotonsillectomy. The study design encompassed administration of morphine using either a calculated dose[3] or a standard dose, both aiming at the attainment of the same level of postsurgical analgesia. These doses were compared to examine (1) which regimen was more efficacious and (2) whether a difference in dose existed between children who had experienced a low preoperative oxygen saturation nadir and those who had not.

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Materials and Methods

The study received approval from the Institutional Review Board of the Montreal Children's Hospital Research Institute, Montreal, Quebec, Canada. Informed parental consent and assent from children aged 7 yr or older were obtained. Children scheduled to undergo elective adenotonsillectomy were recruited to the study if a nocturnal oximetry or a cardiorespiratory study supported the diagnosis of OSA. To recruit the spectrum of OSA severity, a stratified design was used, with two levels of oxygen desaturation: a saturation nadir of < 85%, or a saturation nadir of ≥ 85% and/or an apnea/

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hypopnea index of more than 1 event/h. This grouping, representing severe and moderate/mild OSA, respectively, was based on our report that oxygen saturation nadir of < 85% was predictive of respiratory complications after adenotonsillectomy.[7]

Inclusion criteria for the study comprised an age range of 1.5–10 yr and the absence of other medical conditions. The children were studied only if they met all health criteria by the physical status I definition of the American Society of Anesthesiologists. In addition, symptoms of upper respiratory tract infection, including coryza, excluded the children from the study.

The children were not medicated before surgery. All underwent tracheal intubation and were ventilated and maintained at normocapnic levels throughout surgery. All children received the same anesthesia regimen, including induction with sevoflurane, 10 μg/kg intravenous atropine, 2–4 mg/kg propofol, 0.4 mg/kg rocuronium, 1 μg/kg fentanyl, and 0.5 mg/kg dexamethasone, 40 mg/kg rectal acetaminophen, and isoflurane in nitrous oxide for anesthesia maintenance. The children also received intravenous neostigmine and atropine before extubation and were extubated after awakening in the operating room. All children were operated on by one of two staff surgeons who used similar surgical techniques.

Children received postoperatively one of two morphine regimens: (1) the standard morphine dose, *i.e.*, 50% of 0.1 mg/kg (in accordance with The Montreal Children's Hospital pediatric practice), or (2) a calculated morphine dose derived from the correlation of oxygen saturation nadir and age to the total analgesic morphine required,[3] *i.e.*, 50% of [0.0007 · age (months)] + [0.0021 · saturation nadir (%)] − 0.1138 mg/kg. Each morphine dose was diluted in 4 ml saline solution and injected into the distal injection port of an intravenous line located 1.3 ml from the child's hand. Randomization was achieved by a sealed assignment of the morphine regimen that each child would receive. This assignment was sealed in envelopes that were segregated into the two OSA severity groups and shuffled. All investigators (except I.L., who was given the tasks of randomization and morphine preparation) were blinded to the assigned morphine regimen.

For the purpose of assessing respiratory-related indices postoperatively, Respitrace bands (Respitrace Plus; Non-Invasive Monitoring Systems, Miami Beach, FL) and an oximeter probe (Nellcor 200; TYCO, Mansfield, MA) were applied while the child was still under anesthesia in the operating room. A transcutaneous carbon dioxide probe (Linde MicroGas 7650; Linde Medical Sensors, Basel, Switzerland) was placed after arrival at the postanesthesia care unit. The analog signals of the ribcage and abdominal movements from the Respitrace Plus were amplified and filtered with Bessel filters (Frequency Devices 900; Haverhill, MA) using a cutoff frequency of 12 Hz. The analog signals of the ribcage and abdominal movements, finger plethysmographic pulse waveform, oxygen saturation, and transcutaneous carbon dioxide were digitized, sampled at 50 Hz, and recorded continuously using LABDAT (RHT-Infodat Inc., Montreal, Quebec, Canada).

The protocol of the study, conducted in room air, involved behavioral assessment of pain using the Children's Hospital of Eastern Ontario Pain Score (CHEOPS)[8] after admission into the postanesthesia care unit and every 7 min thereafter. Morphine was administered repeatedly every 7 min until a CHEOPS of 6 was attained. At that score level, the children were behaviorally asleep. The total dose of morphine that was required to achieve the CHEOPS of 6 was the product of the number of injections and the morphine dose in each, from hereon referred to as the total analgesic morphine dose. After the attainment of a CHEOPS of 6, pain levels were assessed hourly, or after the child's awakening. Such awakening denoted the end of the study.

Data Analysis and Statistics

The children included in this study were sorted by their preoperative oxygen saturation nadir into two groups: < 85% and ≥ 85%. The sample size for this study was calculated by power analysis from the difference in total analgesic morphine dose between the same study groups in the retrospective study,[3] in which the < 85% and ≥ 85% groups displayed means ± SD of 0.062 ± 0.040 and 0.105 ± 0.031 mg/kg, respectively. From these, the calculated effect size (Cohen D) was 1.202, from which, using a two-by-two analysis of variance (< 85% and ≥ 85% groups; standard and calculated doses) and with an α of 0.05, the power calculated was 0.799 for a sample size of 12 children for each oxygen saturation group, and, within each group, 6 children for the standard and 6 for the calculated morphine dose.

The calculated or standard morphine dose per injection and the number of injections, time, and the total analgesic morphine dose required for reaching a CHEOPS of 6 were sorted by group and averaged. One hundred–second averages of respiratory frequency and transcutaneous carbon dioxide tension obtained 15 min after attaining a CHEOPS of 6 were also sorted by group and averaged. After a confirmation of variance homogeneity (Levene test) and of normality (Kolmogorov-Smirnov normality test), differences among the groups were analyzed with a two-factor analysis of variance (oxygen saturation nadir by standard/calculated morphine dose). When group differences or interactions were identified, the analyses of variance were followed by *post hoc* pairwise comparisons (Duncan test). One exception was the comparison among morphine doses per injection. In that case, because the standard dose was the same for all patients, the comparison was made nonparametrically using a Kruskal-Wallis test. Sample size was calculated

Table 1. Patients (n = 22), Preoperative Oxygen Saturation Nadir, Apnea/Hypopnea Index, and Morphine Regimen

Patient	Sex	Age, months	Weight, kg	O_2 Saturation Nadir, %	Apnea/Hypopnea Index, events/h	Morphine Regimen
1	M	53	20.5	92	2.5	C
2	F	32	16.7	92	12.2	C
3	M	65	17.0	92	15.8	S
4	F	29	15.3	88		S
5	M	72	19.5	87		S
6	M	67	18.0	87	10.0	C
7	M	36	20.8	84		C
8	F	53	20.2	84		C
9	M	46	18.2	83		C
10	M	32	14.0	83		S
11	M	71	18.2	82		C
12	F	38	19.6	80		S
13	F	55	18.2	80		S
14	F	30	13.0	79		S
15	M	22	12.0	74		C
16	M	34	15.0	73		C
17	F	33	14.2	67		C
18	M	79	24.4	64		S
19	M	19	12.2	64		C
20	M	70	27.0	60		C
21	M	49	16.0	51		S
22	M	34	14.8	44		S

The patients are sorted by oxygen saturation nadir. Patient 16 had a 20.7-s central apnea, and patient 21 desaturated once to 89.7%; both resolved spontaneously.

C = calculated morphine dose; S = standard morphine dose.

with SAS (version 6; SAS Institute, Cary, NC). All other statistical analyses were done with Statistica (version 6; Statsoft, Tulsa, OK). Results are presented as mean ± SEM throughout, and significance was defined at $P \leq 0.05$ for all analyses.

Results

The study took place between April 1, 2004, and November 20, 2005. Three parents refused to give their consent for the study. Important characteristics of each child, including age, weight, preoperative oxygen saturation nadir and/or apnea/hypopnea index, and the blinded assignment to receive either the calculated[3] or the standard morphine dose are presented in table 1. Figure 1 shows the relation between oxygen saturation nadir and total analgesic morphine dose for each of the children included in this study. The results were sorted by OSA severity into < 85% (16 children) or ≥ 85% (6 children) oxygen saturation nadir groups. Within each OSA severity group, the results were further sorted by calculated or standard morphine dosage (see table 1 for group assignment). There were no age differences among these groups.

The calculated and standard total analgesic morphine doses, sorted into < 85% or ≥ 85% oxygen saturation nadir groups, are shown in figure 2A. When the data from the calculated and standard total analgesic morphine doses were combined within each oxygen saturation nadir group, the difference between the two patient groups was significant ($P = 0.014$) in that the < 85% group required approximately half the dose as compared with the ≥ 85% group. *Post hoc* comparisons indicated that both the calculated and the standard total analgesic morphine doses in the < 85% group were lower ($P < 0.05$) than the calculated total analgesic morphine dose in the ≥ 85% saturation nadir group (fig. 2A). There was no difference between the calculated and standard total analgesic doses within either the < 85% or the ≥ 85% oxygen saturation nadir group (fig. 2A).

There were group differences in the morphine dose per injection ($P = 0.014$) (fig. 2B) as well as a difference ($P <$

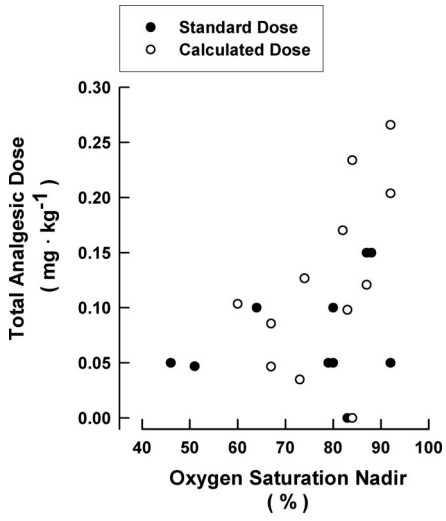

Fig. 1. Total analgesic morphine dose in relation to oxygen saturation nadir for each of the 22 children included in the study. *Filled symbols* depict the standard morphine regimen, and *open symbols* depict the calculated morphine regimen.

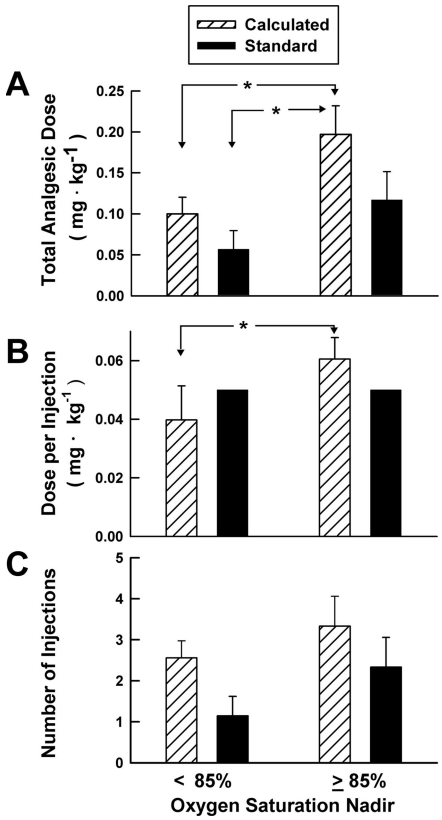

Fig. 2. Mean ± SEM of total analgesic morphine dose (*A*), morphine dose per injection (*B*), and number of morphine injections (*C*) in children with obstructive sleep apnea after adenotonsillectomy. The results are grouped by severity of obstructive sleep apnea into those in children who had a preoperative oxygen saturation nadir of < 85% or ≥ 85%. Within each group, children who received the calculated morphine regimen for analgesia are designated by the *hatched bar*, and those who received the standard pediatric morphine regimen are designated by the *filled bar*. * *Post hoc* differences between groups.

0.05) in the calculated dose per injection between the < 85% and the ≥ 85% study groups (fig. 2B). There were no differences in the number of injections required for analgesia between the oxygen saturation nadir study groups ($P = 0.06$) or between the calculated and standard morphine doses within each oxygen saturation nadir group (fig. 2C). The time required to attain the CHEOPS of 6 did not differ between the < 85% and ≥ 85% study groups or between the calculated and standard morphine dose within each oxygen saturation nadir group (results not shown).

The computerized respiratory-related data were recorded for 131.8 ± 58.2 min. Transcutaneous carbon dioxide levels and respiratory frequency, measured 15 min after the attainment of the target CHEOPS of 6, are presented in table 2. No differences were found among the groups in any of these variables. A single episode of central apnea lasting 20.7 s (table 1, patient 16) and a single episode of oxygen desaturation to 89.7% (table 1, patient 21) were observed postoperatively.

Discussion

The current study was conducted in children with OSA stratified into those who had a history of significant recurrent hypoxemia (< 85% oxygen saturation nadir) and those who had not experienced such hypoxemia (≥ 85% oxygen saturation nadir), all undergoing adenotonsillectomy. The study attempted to gauge the required postoperative analgesic morphine dose by two approaches, one using a standard pediatric morphine dose and the other using a dose calculated from the correlation between oxygen saturation nadir and age on the one hand and morphine requirement on the other.[3]

In evaluating the findings from the current study, several methodologic considerations should be mentioned. (1) In the attempt to stratify the recruitment of children into the study according to the severity of OSA as defined by the oxygen saturation nadir, the most difficult patients to identify for recruitment were those with mild OSA. This is because that group often did not display any oxygen desaturation by oximetry and therefore required polysomnography for diagnosis. Of those children who underwent polysomnography, some were never scheduled for surgery, some were scheduled for surgery with a long delay, some declined to participate in the study, and some were lost to follow-up. However, even with the small sample size in that group, important differences emerged between the two oxygen nadir groups. (2) Because of potential respiratory complications in children with previous oxygen desaturation,[2,5–7] the investigators had to be aware of the

Table 2. Transcutaneous Carbon Dioxide Tension and Respiratory Frequency 15 min after Attaining a CHEOPS of 6 in Children Who Had Undergone Adenotonsillectomy for Obstructive Sleep Apnea

Oxygen Saturation Nadir Groups	< 85%		≥ 85%	
Morphine Dosing	Calculated	Standard	Calculated	Standard
Number of children	9	7	3	3
Transcutaneous carbon dioxide tension, mmHg	45.8 ± 1.8	51.7 ± 1.9	47.3 ± 1.4	45.1 ± 1.7
Respiratory frequency, breaths/min	17.0 ± 1.4	19.1 ± 2.0	16.8 ± 1.2	12.6 ± 1.8

Values are mean ± SEM.

CHEOPS = Children's Hospital of Eastern Ontario Pain Score[8]; morphine dosing = morphine dose per injection by either a calculation from the equation described in the Materials and Methods, or in accordance with the standard dose, 0.05 mg/kg.

severity of OSA in each child before the adenotonsillectomy. Nevertheless, the investigators (except for I.L.) were blinded to the postsurgical morphine dosing method and regimen. (3) In pediatric practice, the reliability of behavioral pain scoring may be complicated by the child's age, native language, unhappiness with the intravenous line and/or respiratory-related apparatus, and by parental separation anxiety. To mitigate these factors, the youngest age included was 1.5 yr, and the children were assessed either while in their parents' laps or with the parents at the bedside. (4) The continuity of the transcutaneous carbon dioxide measurement was disrupted by excessive body movements or by a reluctance of some young children to wear the sensor while awake, both requiring frequent reapplication of the probe. However, the transcutaneous carbon dioxide and respiratory timing values included in the results were those collected 15 min after the attainment of the target CHEOPS of 6, at which time the children were behaviorally asleep and motionless, thus allowing stable recordings.

The lack of any difference in total analgesic morphine dose, morphine dose per injection, number of injections, or time to reach CHEOPS of 6 between the standard and the calculated doses within the $< 85\%$ or the $\geq 85\%$ oxygen saturation nadir groups confirms the soundness of the individualized calculated morphine dose from the correlation equation in our retrospective study[3] and, at the same time, justifies the use of the more straightforward standard pediatric morphine dose.

The current study shows that the postsurgical total analgesic morphine dose required for children with a history of significant recurrent hypoxemia is lower than that in children who have not experienced such hypoxemia. This discrepancy is best seen in the twofold difference in the calculated total analgesic morphine dose between the $< 85\%$ and $\geq 85\%$ oxygen saturation nadir groups, resulting from a difference in the calculated dose per injection between these groups. The reduced total analgesic morphine dose in children with previous hypoxemia is an important finding because it demonstrates that such children display a greater analgesic sensitivity to subsequent opiates than children who had not experienced recurrent hypoxemia. These findings confirm those from our previous study[3] and are strengthened further, because the previous study was retrospective, whereas the current study is prospective, stratified, and blinded in its design. The striking difference in analgesic morphine requirement between children with a history of severe *versus* mild hypoxemia is important in that it behooves clinicians to determine the level of hypoxemia in each child diagnosed with OSA before adenotonsillectomy to adjust the postsurgical analgesic morphine regimen to that level. The advantage of the individualized dosing of morphine in the current study is evident from the lack of postsurgical respiratory complications and from the equal levels of transcutaneous carbon dioxide tension and respiratory frequency across all study groups, indicating an absence of morphine-induced postsurgical hypoventilation in the children with the severe previous hypoxemia.

Although recent guidelines suggest stratification of OSA severity by the apnea/hypopnea index,[1] an assignment of OSA severity by this index alone may underestimate the severity of the OSA. The assessment of OSA by oxygen saturation reveals the range of severity of OSA. Moreover, oximetry requires small, mobile equipment that is simple to use and that can be used in the child's home. Such home recording enhances the accuracy of measurement due to improved sleep quality and can be made in children living at a distance from the sleep laboratory, because the results can be transmitted electronically for analysis and interpretation. Because of these considerations, we maintain the approach of primarily establishing the diagnosis of suspected OSA by oximetry.[7]

From the current findings, we propose that opiate management postsurgically in patients with OSA should be carefully titrated to the previous hypoxemia level in each patient. We anticipate that in those patients with OSA and significant previous hypoxemia during sleep, the total analgesic opiate dose that will be sufficient to ensure adequate analgesia will be one half of that required in patients with no such history. We also believe that the tailoring of the opiate regimen to the child's previous oxygen desaturation may diminish postsurgical respiratory complications.

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