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# ACUTE & PERIOPERATIVE PAIN SECTION

## *Original Research Articles*

# Opioid-Related Adverse Effects in Children Undergoing Surgery: Unequal Burden on Younger Girls with Higher Doses of Opioids

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This pharmacogenetic study was designed and undertaken by the authors.

**Abstract**

**Objective. Unpredictable interindividual variability in response to opioids results in inadequate analgesia and opioid-related adverse effects. The effects of the child's sex on opioid response have not been well studied. The aim of this study is to determine the effects of sex on opioid-related adverse effects in children undergoing tonsillectomy.**

**Design. Prospective observational clinical study.**

**Setting. Outpatient pediatric surgery.**

**Subjects. Two hundred and seventy five children between 6 and 15 years of age undergoing outpatient tonsillectomy.**

**Methods. All children received standard perioperative care with a standard intraoperative dose of morphine. Opioid-related analgesia and safety outcomes included incidences of respiratory depression (RD), postoperative nausea and vomiting (PONV) and incidence of prolonged stay in the, post-anesthesia recovery unit (PACU) due to opioid related adverse effects.**

**Results. Given the small sample of minority population, we focused our study on 219 white children. Significant morphine effect was observed in girls but not boys for PONV (P = 0.001) and prolonged PACU stay due to PONV (P = 0.010). Although the overall incidence of RD is not statistically different between boys and girls, the incidence of RD (52% vs 32%) and PONV (43% vs 4%) tended to be more in white girls than boys as**

**the total perioperative morphine dose increased to 0.3 mg/kg or more.**

**Conclusions. This study demonstrates that child's sex influences morphine's dose response and adverse effects. White girls have an unequal burden with higher incidences of PONV, RD, and prolonged PACU stays following tonsillectomy from PONV and RD as total morphine doses are increased.**

**Key Words. Opioids; Respiratory Depression; PONV; Sex Differences; Tonsillectomy; Analgesia**

## Introduction

Opioids are the most common analgesics used to manage acute postoperative pain in children and adults [1]. Although opioids are highly effective in treating pain, their use frequently results in various side effects including nausea and vomiting, pruritus, constipation, sedation as well as potentially fatal respiratory depression (RD) in children [2]. Wide variations in interindividual response and narrow therapeutic indices of opioids make clinical practice challenging as it is difficult to optimize opioid selection and dosing by proactively predicting an individual child's responses. In our previous study, we have reported that a child's race influences opioids' responses with an unequal burden of opioid-related adverse effects in white children and poorly controlled postoperative pain in African American children following tonsillectomy [3].

Multiple studies have examined the impact of sex on opioid responses with disparate results. A recent review concluded that adult females have higher sensitivity to both clinically and experimentally induced pain [4]. Clinical studies of factors affecting morphine induced pain relief have consistently shown that adult males required higher doses of morphine for similar levels of pain relief after abdominal and orthopedic surgeries [5,6]. Use of experimental pain models to evaluate sex differences in morphine response have shown no sex differences in analgesia, but a higher incidence of opioid-related adverse effects in healthy adult women volunteers, compared with men [7]. Although a large number of preclinical and experimental studies indicate differences in pain modulation between rodent males and females and adult humans in terms of increased pain and opioid sensitivity in females, clinical trials investigating postoperative pain and sex differences are inconsistent [4]. Moreover, the data with sex differences related to opioid analgesics from adult human trials are not sufficient to reliably guide pediatric clinical practice [8]. There are no clinical studies in children to study sex-specific responses to opioids in terms of analgesic and adverse effects.

Study of sex differences in morphine effects in the pediatric population is especially important, as the mechanisms underlying them are likely influenced by physiological, developmental and hormonal factors, which may vary

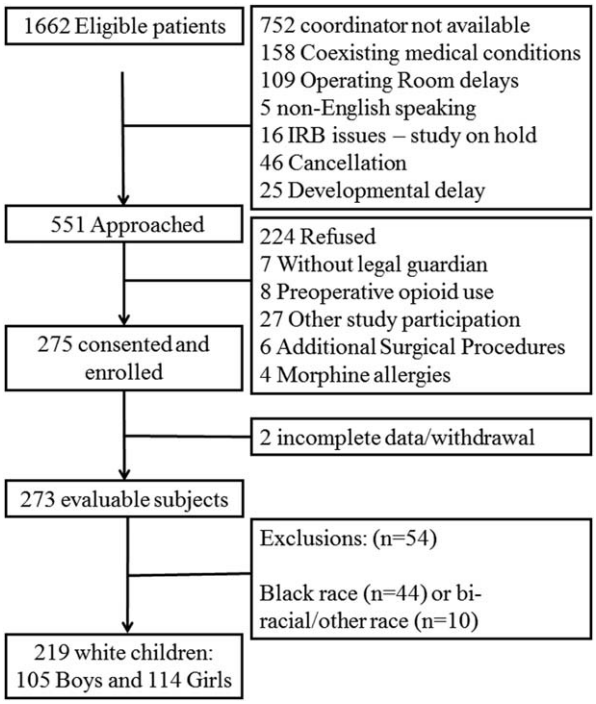



**Figure 1** The consort diagram illustrates the flow of study participants through this clinical trial. Eligible participants, reasons for exclusions, and enrolled patients are reported. IRB = institutional review board.

**Table 1** Demographic characters and perioperative morphine use

| | Female (N = 114) | | Male (N = 105) | | *P* Value |
|---|---|---|---|---|---|
| Age (year) | 8.4 | (7.1, 11.6) | 8.4 | (6.9, 10.4) | 0.16 |
| Weight (Kg) | 36.1 | (26.0, 48.0) | 33.3 | (25.8, 43.6) | 0.25 |
| BMI *z* score | 0.9 | (−0.2, 1.6) | 0.6 | (−0.2, 1.6) | 0.93 |
| Intra-op morphine (mg/kg) | 0.19 | (0.16, 0.21) | 0.19 | (0.18, 0.21) | 0.42 |
| Total morphine (mg/kg) | 0.23 | (0.19, 0.29) | 0.25 | (0.20, 0.29) | 0.13 |
| Age group | | | | | |
| > 13 year | 15 | (13%) | 8 | (8%) | 0.39 |
| 8–13 year | 52 | (46%) | 49 | (47%) | |
| < 8 year | 47 | (41%) | 48 | (46%) | |
| Intra-op morphine group | | | | | 0.86 |
| 0.1–0.2 mg/kg | 71 | (62%) | 68 | (65%) | |
| >0.2 mg/kg | 43 | (38%) | 37 | (35%) | |
| Total morphine group | | | | | 0.71 |
| < 0.2 mg/kg | 41 | (36%) | 33 | (31%) | |
| 0.2–0.3 mg/kg | 50 | (44%) | 47 | (45%) | |
| > 0.3 mg/kg | 23 | (20%) | 25 | (24%) | |
| OSA | | | | | 0.04 |
| No | 57 | (50%) | 67 | (64%) | |
| Yes | 57 | (50%) | 38 | (36%) | |

BMI *z* score was calculated using the CDC growth charts.

Age, weight, BMI *z* scores, intra-op morphine and total morphine requirement are shown as median and IQR for entire study cohort, and compared using Wilcoxon rank sum test; Age group, intraoperative and total morphine groups, and OSA are shown as number and proportions, and compared using Pearson chi-square test.

OSA = Obstructive Sleep Apnea.

between prepubertal children, adolescents and adults. Compared with adults with different comorbid conditions undergoing different surgeries and receiving different perioperative medications, a relatively large number of healthy children undergoing one type of surgery with standardized perioperative management is a better population to study interindividual variations associated with opioids. We hypothesized that sex of the child affects postoperative analgesic and adverse outcomes with the use of opioids. Therefore, the aim of our study was to determine the role of a child's sex in determining the analgesic property and adverse effects of morphine in children undergoing tonsillectomy. Knowledge about the factors contributing to variable opioid response will help optimize opioid dosing, analgesic outcomes, and inform adverse effect prevention strategies in the future.

## Methods

### *Study Design and Setting*

This was a prospective clinical observational study using a standard perioperative anesthetic and surgical practices and standard postoperative nursing care within the tonsillectomy population evaluating many factors including race [3], genetic variants [9–13], and sex contributing to variability in opioid responses in children. This study was approved by the institutional review board Institutional review board at Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA and written informed consents and assents, when appropriate, were obtained from all parents and participating children. In this project, there was no selection for specific races, however, given the demographics of patients for tonsillectomy or adenotonsillectomy (T/TA) surgery at our hospital, the vast majority of patients were white (Figure 1). While data for multiple races were available, given the small sample sizes of the non-white boys and girls, we focused on white children and examined the effect of sex in white children because our previous research showed differences in opioid related adverse events in children by race with in white children having relatively more adverse effects than black children [3].

### *Participants*

Children 6–15 years undergoing elective outpatient T/TA who were eligible for the study were approached and recruited on the day of surgery between August 2008 and February 2012. Race was self-reported by either the parent or child; self-report is well accepted for identifying race. Sample inclusion criteria were children designated to have an American Society of Anesthesiologists physical status 1 or 2 scheduled for T/TA because of recurrent tonsillitis, adenotonsillar hypertrophy or obstructive sleep apnea (OSA). Clinical criteria for OSA designation included sleep disordered breathing with a history of snoring and either sleep pauses lasting more than 10 seconds or daytime

**Table 2** Sex differences in analgesia and opioid adverse effect outcomes

| | | Obstructive Sleep Apnea | | | | | |
|---|---|---|---|---|---|---|---|
| | | No | | Yes | | All | |
| | | | *P* Value | | *P* Value | | *P* Value |
| Postoperative morphine (mg/Kg) | F | 0.08 ± 0.04 | 0.31 | 0.09 ± 0.06 | 0.89 | 0.09 ± 0.05 | 0.60 |
| | M | 0.09 ± 0.05 | | 0.09 ± 0.05 | | 0.09 ± 0.05 | |
| Maximum NRS pain score | F | 6 (3–9) | 0.25 | 5 (2–9) | 0.92 | 6 (2–9) | 0.38 |
| | M | 6 (3–8) | | 5 (2–8) | | 5 (3–8) | |
| Maximum FLACC pain score | F | 2 (0–4) | 0.84 | 2 (0–5) | 0.08 | 2 (0–5) | 0.25 |
| | M | 2 (0–5) | | 4 (1–7) | | 2 (1–5) | |
| Number of analgesic interventions | F | 1 (0–1) | 0.30 | 1 (0–1) | 0.26 | 1 (0–1) | 0.88 |
| | M | 1 (0–1) | | 1 (0–2) | | 1 (0–1) | |
| Prolonged PACU stay due to pain | F | 21 (17%) | 1.00 | 16 (17%) | 0.82 | 37 (17%) | 0.78 |
| | M | 24 (19%) | | 12 (13%) | | 36 (16%) | |
| Analgesic Intervention need in PACU | F | 35 (28%) | 0.36 | 32 (34%) | 0.28 | 67 (31%) | 1.00 |
| | M | 35 (28%) | | 26 (27%) | | 61 (28%) | |
| RD | F | 9 (7%) | 0.81 | 11 (12%) | 0.79 | 20 (9%) | 1.00 |
| | M | 12 (10%) | | 6 (6%) | | 18 (8%) | |
| PONV | F | 11 (9%) | 0.20 | 11 (12%) | 1.00 | 22 (10%) | 0.28 |
| | M | 7 (6%) | | 7 (7%) | | 14 (6%) | |
| Pruritus | F | 41 (33%) | 0.54 | 47 (50%) | 0.30 | 88 (41%) | 0.75 |
| | M | 51 (41%) | | 28 (30%) | | 79 (36%) | |
| Prolonged stay in PACU due to RD | F | 5 (4%) | 0.77 | 6 (6%) | 0.75 | 11 (5%) | 0.53 |
| | M | 8 (6%) | | 5 (5%) | | 13 (6%) | |
| Prolonged stay in PACU due to PONV | F | 2 (2%) | 0.29 | 8 (8%) | 0.31 | 10 (5%) | 0.81 |
| | M | 6 (5%) | | 2 (2%) | | 8 (4%) | |

Postoperative morphine was shown as mean ± SD, and was compared using *t*-test. It was examined only in patients who needed postoperative morphine.
Number of analgesic intervention, maximum NRS and FLACC scores were shown as median (IQR), and were compared using Wilcoxon rank sum tests.
Dichotomous variables were shown as number of cases (proportion), and were compared using Fisher's Exact test.
F = female; M = male; PACU = post-anesthesia recovery unit; RD = respiratory depression; PONV = postoperative nausea and vomiting.

**Table 3** Sex-specific association of adverse effects and total morphine doses

| | | Total Morphine by Weight (mg/kg) | | | |
|---|---|---|---|---|---|
| | | <0.2 | 0.2–<0.3 | ≥0.3 | |
| | | Number of Cases (%) | Number of Cases (%) | Number of Cases (%) | *P* Value* |
| RD | F | 5 (12) | 3 (6) | 12 (52) | **0.001** |
| | M | 4 (12) | 6 (13) | 8 (32) | 0.079 |
| PONV | F | 4 (10) | 8 (16) | 10 (43) | **0.003** |
| | M | 6 (18) | 7 (15) | 1 (4) | 0.172 |
| Pruritus | F | 29 (73) | 42 (84) | 17 (74) | 0.636 |
| | M | 24 (73) | 35 (76) | 20 (80) | 0.521 |
| Prolonged stay in | F | 2 (5) | 1 (2) | 8 (35) | **0.002** |
| PACU due to RD | M | 5 (15) | 3 (6) | 5 (20) | 0.841 |
| Prolonged stay in | F | 2 (5) | 3 (6) | 5 (22) | 0. 068 |
| PACU due to PONV | M | 4 (12) | 3 (6) | 1 (4) | 0.295 |

*Exact test on the Spearman correlation coefficient.

F = female; M = male; PACU = post-anesthesia recovery unit; RD = respiratory depression; PONV = postoperative nausea and vomiting.

drowsiness; as documented in preoperative surgical note, the indication for tonsillectomy in these children was clinical diagnosis of OSA. Children with severe OSA documented by a sleep study or needing overnight admission and/or breathing support (e.g., BIPAP at night) were not included in this study. Children were excluded from the study if they or their parents were non-English speaking. Children who were allergic to morphine or who had developmental delay, liver or renal disease, or preoperative pain requiring opioid analgesics (e.g., chronic tonsillitis) were excluded. Due to limited availability of research coordinators for this study, we were not able to recruit all eligible subjects (Figure 1).

*Standard Care and Study Procedures*

As part of T/TA standard practice at our institution, all children receive prophylactic ondansetron (0.1 mg/kg) and dexamethasone (0.1 mg/kg) intraoperatively. Anesthesia is induced via sevoflurane inhaled induction followed by a propofol (2 mg/kg) bolus to facilitate endotracheal intubation. Anesthesia was maintained with sevoflurane without the use of neuromuscular blockade. Patients receive morphine for pre-emptive analgesia prior to surgical incision. Children with OSA history receive 0.1 mg/kg morphine while those without OSA diagnosis receive 0.2 mg/kg. If there are any signs suggestive of pain (clinically significant increase in heart rate and blood pressure) following surgical incision and cauterization, the clinical anesthesia team provides additional morphine doses of 0.05 mg/kg intraoperatively as necessary.

*Outcome Measures*

Outcomes for analgesic effectiveness and opioid-related adverse effects were collected. Analgesic effectiveness outcomes included postoperative pain scores, morphine doses (mg/kg), need for intravenous analgesic intervention (yes/no), prolonged post-anesthesia recovery unit (PACU) stay (>90 minutes) due to pain (yes/no), and the number of total analgesic interventions given. In addition, subjective and objective pain scores were assessed using a 0 to 10 numerical Rating Scale (NRS) [14] and a 0 to 10 FLACC (facial expression; leg movement; activity; cry; and consolability) scale [15], respectively. Significant postoperative pain (NRS or FLACC $\geq$ 4/10) was managed in the PACU with rescue doses of morphine (0.05 mg/kg). The maximum NRS and FLACC scores were examined.

Adverse effects were measured by two sets of binary outcomes: 1) opioid-related side effects including RD, nausea/vomiting (postoperative nausea and vomiting [PONV]) and pruritus; 2) prolonged PACU stay secondary to RD or nausea/vomiting. In our study, we defined RD as a persistent respiratory rate <10 breaths per minute or persistent oxygen desaturation <92% requiring supplemental oxygen to maintain SpO2 > 92% in the absence of clinically obvious upper airway obstruction and artifacts for 1 minute or longer.

Duration of PACU stay (time to achieve PACU discharge readiness) was defined as the duration in PACU before achieving the following discharge criteria. Level of consciousness: easily arousable or awake, airway: patent with adequate air exchange, core body temperature: $\geq$36.3 °C, acceptable pain level (pain score < 4), hemodynamically stable, no significant opioid related adverse effects such as PONV and RD, and surgical site without any bleeding or complications. This is discharge readiness time is different from actual PACU discharge time as we did not want to include delays due to social reasons (e.g., waiting for car ride, etc).

*Statistical Analysis*

Prior to analyses, data quality was examined. As we had only 44 African Americans and 10 other race, analyses were performed on whites. To assess the sex effect, outcome measurements were first compared between boys and girls with and without OSA stratification. Continuous variables were compared using *t*-test or Wilcoxon rank-sum test and categorical variables were compared using Fisher's exact test. To analyze morphine effects, intraoperative and total morphine doses (mg/kg) were categorized into low, medium, and high (≤0.1, >0.1–0.2, and >0.2 for intraoperative morphine and <0.2, 0.2–0.3, and >0.3 for total morphine). Spearman correlation coefficients were used to assess the relationship between morphine dose and outcomes by sex.

Multivariate statistical modeling was then performed to formally test the sex effect and the interaction of sex and morphine dose while accounting for covariate effects. For analgesic effectiveness outcomes, intraoperative morphine was used as a covariate; for side effects outcomes, total morphine requirement (calculated as the sum of the intra- and postoperative morphine dose) was used as a covariate. Effects of age, weight, BMI *z* scores, and OSA were also tested as covariates for all the outcomes. When significant effects were detected ($P < 0.05$), covariates were included in the final models. Binary outcomes were analyzed using logistic regression. Maximum NRS was analyzed using linear regression. Maximum FLACC score was analyzed by using a zero-inflated negative binomial model because of the inflated frequency of score 0. The total number of analgesic interventions followed a Poisson distribution and was analyzed using a generalized linear model. Postoperative morphine dose was analyzed in patients who needed intervention using a linear regression.

To examine whether the relationship between side effects and total morphine dose differs by age, we grouped female patients into three age groups: less than 8 years, 8 to 13 years, and greater than 13 years of age to classify females as prepubertal, peripubertal, and postpubertal in lieu of formal Tanner staging. In this

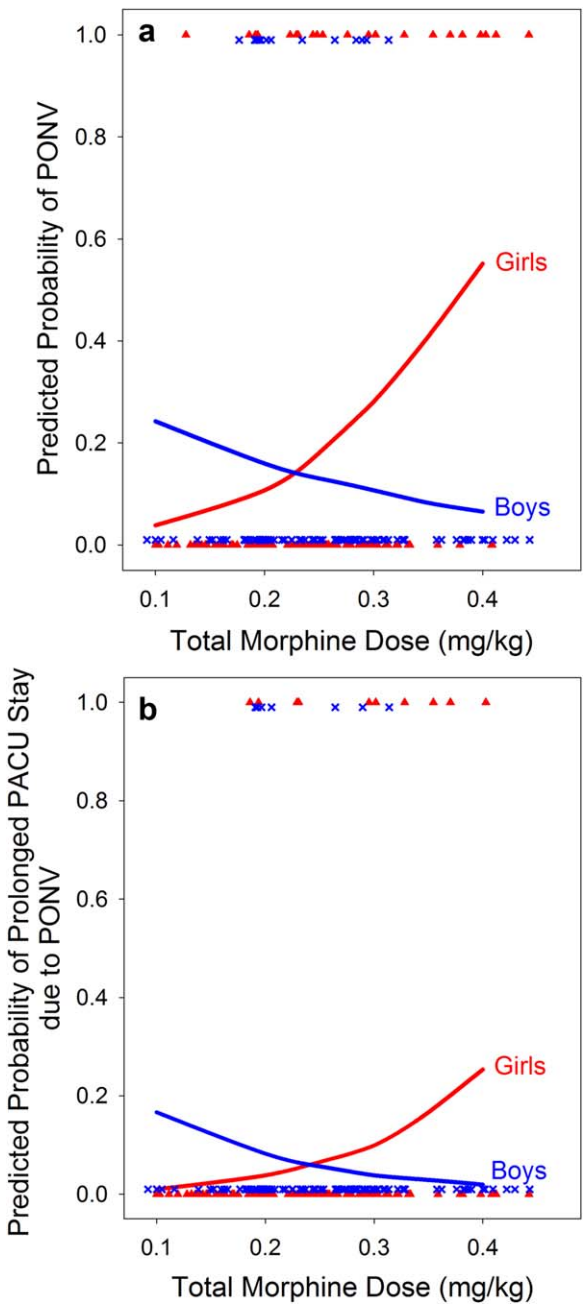



**Figure 2** *a*. Sex-specific differences in morphine related PONV in PACU. Total morphine dose is plotted in the *X*-axis and the probabilities of morphine related PONV are plotted in the *Y*-axis for Boys and Girls. Overall incidences of opioid related PONV in the PACU were relatively higher in girls compared with boys as the total morphine dose increased. *b*. Sex-specific differences in morphine related PONV resulting in prolonged stays in PACU. Total morphine dose is plotted in the *X*-axis and the probabilities of prolonged PACU stay due to PONV are plotted in the *Y*-axis for Boys and Girls. The probability of PONV leading to prolonged PACU stay was relatively higher in girls compared with boys as the total morphine dose increased. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Table 4** Sex-specific association of analgesia and total morphine doses

| | Intra-op Morphine by Weight (mg/kg) | | | | |
|---|---|---|---|---|---|
| ≤0.1 | | >0.1–0.2 | > 0.2 | | |
| Mean ± SD Median (IQR) Number of Cases (%) | | Mean ± SD Median (IQR) Number of Cases (%) | Mean ± SD Median (IQR) Number of Cases (%) | | *P* Value* |
| Postoperative morphine (mg/Kg) | F | 0.07 ± 0.03 | 0.09 ± 0.05 | 0.10 ± 0.05 | 0.09 |
| | M | 0.07 ± 0.04 | 0.10 ± 0.05 | 0.09 ± 0.05 | 0.83 |
| Maximum NRS pain score | F | 8 (6–10) | 5 (2–8) | 6 (3–9) | 0.75 |
| | M | 6 (5–9) | 5 (2–8) | 6 (4–7) | 0.95 |
| Maximum FLACC pain score | F | 3 (3–4) | 2 (0–5) | 1 (0–5) | 0.24 |
| | M | 3 (1–5) | 3 (1–7) | 2 (0–5) | 0.20 |
| Number of analgesic interventions | F | 1 (1–2) | 1 (0–1) | 1 (0–1) | 0.22 |
| | M | 1 (1–2) | 1 (0–1) | 1 (0–1) | 0.40 |
| Prolonged PACU stay due to pain | F | 3 (60) | 22 (33) | 12 (28) | 0.28 |
| | M | 2 (33) | 22 (35) | 12 (32) | 0.85 |
| Analgesic Intervention need in PACU | F | 5 (100) | 40 (61) | 22 (51) | 0.10 |
| | M | 5 (83) | 36 (58) | 20 (54) | 0.35 |

*Exact test on the Spearman correlation coefficient.

Postoperative morphine was shown as mean ± SD, and was examined in patients who needed morphine postoperation.

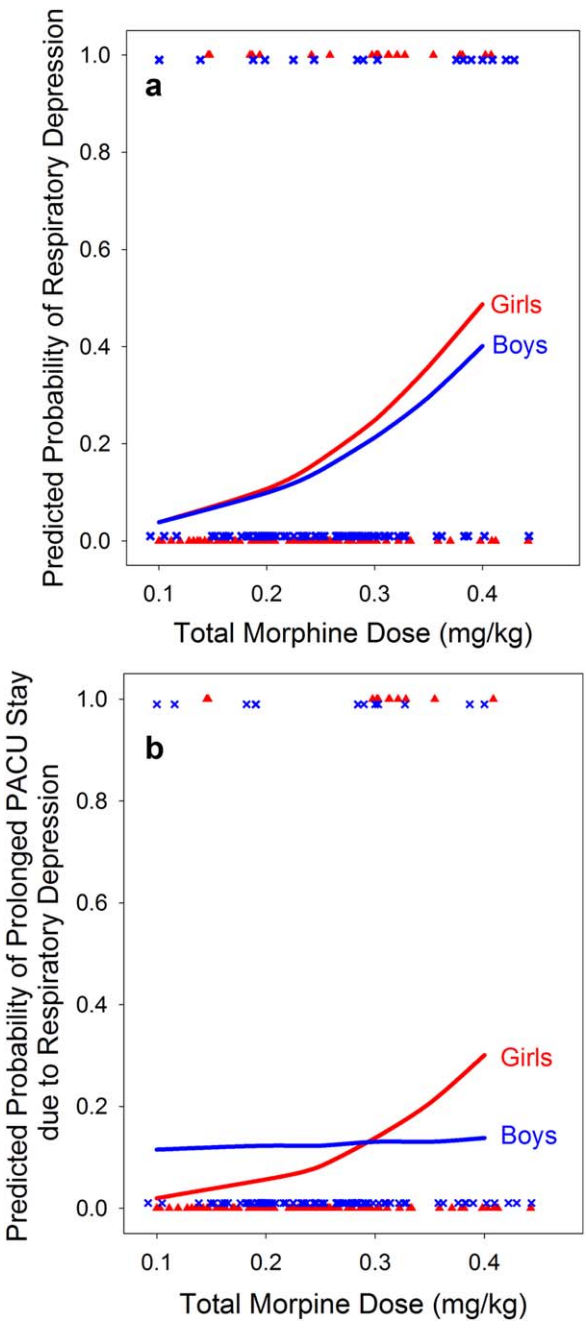
Number of analgesic intervention, maximum NRS and FLACC score was shown as median (IQR).

Dichotomous variables were shown as number of cases (proportion).

F = female; M = male; PACU = post-anesthesia recovery unit; NRS = numerical rating scale.

analysis, total morphine requirement was dichotomized into ≥0.3 or <0.3 mg/kg dose ranges because of a potential threshold effect of morphine. The linear trends between total morphine and PONV, RD, prolonged PACU due to PONV and RD were assessed separately in the three age groups. This hypothesis was then formally tested using multivariate logistic models.

Statistical analyses were performed using Statistical Analysis Software, version 9.3 (SAS Institute Inc., Cary, NC). We examined 11 correlated outcomes with mean Spearman correlation coefficient of 0.26. A correlation adjusted Bonferroni correction (http://www.quantitativeskills.com/sisa/) yielded a significance threshold of 0.008. We also reported association reaching the threshold of 0.05. This may help to identify potential associations for future studies, but caution has to be taken when interpret these results due to the inflated type I error rate.




## Results

### *Demographics*

A consort diagram illustrates eligible, approached, and enrolled study subjects (Figure 1). Due to relatively smaller sample sizes of non-white children (44 African Americans and 10 other races or biracial), we focused on 219 white children (114 girls and 105 boys). Although mean age and weight were comparable, girls had a higher incidence of OSA (50% vs 36%, $P = 0.04$) (Table 1). Age and BMI were comparable between boys and girls.

### *Overall Analgesia and Safety Outcomes and Effect of Sex*

When all doses of total morphine were grouped together, no significant differences were detected in any of the analgesia and opioid related adverse outcomes in univariate analyses (Table 2) or multivariate modeling (data not shown). Stratifying by OSA did not affect these results.

### *Differential Morphine Dose Related PONV, and Prolonged PACU Stays by Sex*

Although no overall differences in side effects were observed by sex, in girls, opioid related adverse effects

**Figure 3** *a*. Sex-specific differences in morphine related RD in PACU. Total morphine dose is plotted in the *X*-axis and probability of morphine related RD is plotted in the *Y*-axis for Boys and Girls. Overall incidences of opioid related RD in the PACU were relatively higher in girls compared with boys as the total morphine dose increased. *b*. Sex-specific differences in morphine related RD resulting in prolonged stays in PACU. Total morphine dose is plotted in the *X*-axis and the probabilities of prolonged PACU stay due to RD are plotted in the *Y*-axis for Boys and Girls. The probability of PONV leading to prolonged PACU stay was relatively higher in girls compared with boys as the total morphine dose increased. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Table 5** Opioid related adverse effects in younger vs older girls by total morphine group

| | | Total Morphine by Weight (mg/kg) | | |
|---|---|---|---|---|
| | | <0.3 | >=0.3 | |
| Opioid-Related Adverse Effects | Age in Years | Number of Cases (%) | Number of Cases (%) | *P* Value* |
| RD | >13 | 1 (9) | 2 (50) | 0.15 |
| | 8–13 | 4 (9) | 5 (56) | 0.0045 |
| | <8 | 3 (8) | 5 (50) | 0.0067 |
| Prolonged stay in PACU due to RD | >13 | 0 (0) | 1 (25) | 0.27 |
| | 8–13 | 1 (2) | 3 (33) | 0.0138 |
| | <8 | 2 (5) | 4 (40) | 0.0139 |
| PONV | >13 | 1 (9) | 2 (50) | 0.15 |
| | 8–13 | 4 (9) | 2 (22) | 0.57 |
| | <8 | 7 (19) | 6 (60) | 0.0175 |
| Prolonged stay in PACU due to PONV | >13 | 1 (9) | 0 (0) | 1.00 |
| | 8–13 | 2 (5) | 1 (11) | 1.00 |
| | <8 | 2 (5) | 4 (40) | 0.0139 |

*Exact test on the Spearman correlation coefficient.

PACU = postanesthesia recovery unit; PONV = postoperative nausea and vomiting.

tended to occur more often when high total morphine dose (>0.3 mg/kg) was administered, while in boys, linear trends were either attenuated or abolished (Table 3). Taken together, these data indicate a sex-specific morphine effect on all opioid side effects except for pruritus. The univariate analyses were supported by multivariate models which formally tested for a morphine effect by sex using total morphine as a continuous variable. Significant sex-specific morphine effect was detected in PONV ($P = 0.001$) and prolonged PACU stay due to PONV ($P = 0.010$). In girls, probabilities of having these adverse effects increased with the total morphine dose, while in males, no significant changes were detected in the probabilities of having adverse effects with the increase of total morphine dose (Figures 2a and 2b). Data shown in Table 3 suggested that in girls, most side effects occurred when total morphine exceeded 0.3 mg/kg. We tested the threshold morphine effect using multivariate models. The probability of side effects did not differ between the two lower morphine groups. However, when morphine exceeded 0.3 mg/kg, the probability of all opioid adverse effects except for pruritus increased significantly ($P < 0.05$).

### *Higher Morphine Dose Related RD in Girls*

In girls, probabilities of having RD increased with increase in total morphine dose ($P = 0.001$) (Figures 3a and 3b). In boys, no significant changes were detected in the probabilities of having RD with the increase of total morphine dose ($P = 0.079$, Table 3). In younger girls (<8 years and 8–13 years), significant association was detected between RD and higher total morphine dose (≥0.3 mg/kg; Table 5).

### *Differential Morphine Dose Dependent Length of PACU Stays by Sex*

White girls who received ≥0.3 mg/kg of total morphine stayed longer in PACU ($111 \pm 6.6$ minutes) than that of girls who received <0.3 mg/kg of total morphine ($82.2 \pm 3.3$ minutes) (Figure 4). White boys who received ≥0.3 mg/kg of total morphine stayed in PACU for $99.7 \pm 6.4$ minutes, while boys who received <0.3 mg/kg of morphine stayed in PACU for $88.3 \pm 3.6$ minutes (Figure 3). Although the differences in durations in PACU discharge readiness did not reach statistical significance ($P = 0.09$) after adjusting for age, weight, history of OSA, about 30 minutes of longer stay in white girls who received higher total morphine doses compared with lower doses, is clinically and economically significant (about US$160 more direct PACU charges for >30 minutes longer PACU stay in girls) following outpatient tonsillectomy. In the analysis stratified by sex, girls with high dose had longer PACU stay than girls with low dose ($P = 0.0002$); however in boys, the difference is not statistically significant ($P = 0.11$; Figure 4). There was a trend toward longer prolonged PACU stay in girls with high morphine dose than boys ($P = 0.09$), although it did not attain statistical significance.

### *No Differential Response to Morphine with Respect to Analgesic Effectiveness by Sex*

There was no evidence of sex-specific morphine effects on analgesic outcomes using either the univariate or multivariate modeling (Table 4).

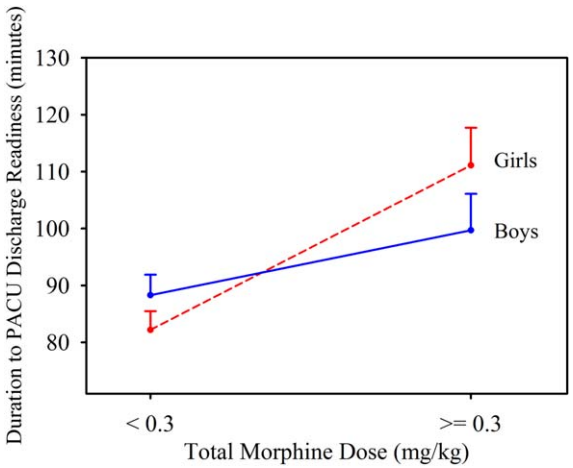



**Figure 4** Sex-specific differences in duration of stays in PACU between low (<0.3 mg/kg) and high (≥0.3 mg/kg) total morphine doses. White girls who received ≥0.3 mg/kg of total morphine stayed longer in PACU (111.1 ± 6.6 minutes) than that of girls who received <0.3 mg/kg of total morphine (82.2 ± 3.3 minutes). White boys who received ≥0.3 mg/kgof total morphine stayed in PACU for 99.7 ± 6.4 minutes, while boys who received <0.3 mg/kg of morphine stayed in PACU for 88.3 ± 3.6 minutes. Although the differences in durations in PACU stay is clinically significant with about 30 minutes of longer stay in white girls between low and high total morphine doses, it did not reach statistical significance ($P$ = 0.09) after adjusting for age, weight, history of OSA. Even though the prolonged PACU stay in girls with high dose does not differ from that in boys with statistical significance ($P$ = 0.09), in the analysis stratified by sex, girls with high dose had longer PACU stay than girls with low dose ($P$ = 0.0002). But in boys, the difference is not statistically significant ($P$ = 0.11). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

### *Morphine Effect on Safety Outcomes is Independent of Age in Girls*

In girls, significant association of total morphine dose was detected with PONV, RD, prolonged PACU due to PONV and RD. To test whether this association is influenced by age (i.e., hormonal effect in postpubertal girls), we compared girls who were less than 8 years, 8 to 13 years, and greater than 13 years (Table 5). Surprisingly, younger prepubertal girls (<8 years and 8–13 years) showed significant associations with RD, PONV, and prolonged PACU stays; and older girls (>13 years) did not have similar associations (Table 5). However, when the age effect alone was tested in multivariate models, there was no statistically significant age differentiation detected possibly due to small sample size (data not shown). In addition, similar to girls, we compared boys who were less than 8 years, 8 to 13 years, and greater than 13 years (Table 6). However, there was no significantly higher incidence of opioid adverse effects in younger boys compared with older boys between lower and higher doses of morphine (Table 6), unlike young girls receiving >0.3 mg/kg of morphine (Table 5).

## Discussion

This study demonstrates that while having similar analgesia, white girls were more sensitive to opioid adverse effects than boys as total morphine dose increased. White girls have differential response to higher total morphine doses leading to an unequal burden of higher incidences of opioid related adverse effects and prolonged hospital stays after outpatient surgery compared with boys. Specifically, increasing doses of morphine in girls was associated with increased RD, PONV, and prolonged stay in the recovery room due to opioid-related RD and PONV compared with boys. When not stratified by total morphine to low, medium, and high doses, the safety and analgesic outcomes with the perioperative use of morphine in children did not differ by sex. These findings were not associated with age, BMI, and surgical technique. These findings have significant clinical and economic impacts as girls are likely to have more opioid related RD and PONV with higher doses of opioids leading to longer hospital stays as compared with boys.

We found that increasing morphine doses resulted in increased side effects in girls but not boys. Specifically, girls who received the highest morphine dose category (0.3 mg/kg) had significantly more RD, PONV, prolonged PACU stay due to RD, and prolonged PACU stay due to PONV compared with those not in the high category. However, morphine dose was not associated with side effects in boys. The duration of PACU stay due to opioid adverse effects (Figure 4), was significantly different girls getting low and high doses ($P$ = 0.0002), and it was not the case in boys ($P$ = 0.11). The comparison between boys and girls on duration of PACU stay due to opioid adverse effects between low and high doses of morphine is clinically significant with about 30 minutes of longer PACU stay in girls than boys, and there was a trend toward statistical significance ($P$ = 0.09). Longer PACU stays in girls compared with boys is not only clinically important and it is also associated additional economic burden due to additional costs associated with prolonged PACU stays. Based on our research data, estimated additional direct PACU charges would be approximately US$160 more for girls compared with boys for the same tonsillectomy surgery because of adverse effects due to higher doses of opioids. Importantly, these effects were not related to

**Table 6** Opioid related adverse effects in younger vs older boys by total morphine group

| | | Total Morphine by Weight (mg/kg) | | |
|---|---|---|---|---|
| | | <0.3 | ≥0.3 | |
| Opioid-Related Adverse Effects | Age in Years | Number of Cases (%) | Number of Cases (%) | *P* Value* |
| RD | >13 | 0 (0) | 0 (0) | – |
| | 8–13 | 5 (14) | 4 (33) | 0.19 |
| | <8 | 5 (14) | 4 (36) | 0.18 |
| Prolonged stay in PACU due to RD | >13 | 1 (17) | 0 (0) | 1.00 |
| | 8–13 | 4 (11) | 2 (17) | 0.63 |
| | <8 | 3 (8) | 3 (27) | 0.12 |
| PONV | >13 | 0 (0) | 0 (0) | – |
| | 8–13 | 6 (16) | 0 (0) | 0.31 |
| | <8 | 7 (19) | 1 (9) | 0.66 |
| Prolonged stay in PACU due to PONV | >13 | 0 (0) | 0 (0) | – |
| | 8–13 | 3 (8) | 0 (0) | 0.57 |
| | <8 | 4 (11) | 1 (9) | 1.00 |

*Exact test on the Spearman correlation coefficient.

PACU = post-anesthesia recovery unit; PONV = postoperative nausea and vomiting.

OSA despite a relatively higher incidence of OSA in girls in our cohort. In the adult population, the literature supports that compared with men, women experience higher rates of opioid-related adverse effects, including RD [7,16–19]. A few adult studies that looked at sex differences with morphine-induced RD [20–22] showed that as compared with men, women are at higher risk of developing RD. However, very little data exists examining the effects of sex on opioid-related adverse effects in children.

In our extended postdischarge follow-up of the study cohort, we have observed that girls with functional CYP2D6 phenotypes had significantly higher incidence of adverse effects at home with oral codeine (morphine prodrug) in the first 2–3 postoperative days similar and consistent to higher intravenous morphine dose related adverse effects among girls in PACU before discharge [23]. These consistent findings of higher incidences of adverse effects with intravenous morphine and oral codeine among girls in the hospital and home setting besides confirming the findings show the extended and unequal clinical and potentially economic impacts of opioids on girls. Sex related difference in RD is shown to be secondary to effects mediated by the peripheral chemoreflex loop as opposed to a centrally mediated effect [21].

Our study did not find any association between sex, morphine dose and analgesia. We also did not find a differential association of pain by pubertal age categories in girls. This is in contrast to some human adult studies which suggest that women experience better pain control with opioids [24]. The entire pain experience may have different perception based upon sex [25]. In addition, a significant difference in pharmacokinetics (~40%) exists between men and women and it is attributed to a lower total body water as well as higher fat percentage to muscle in women than men [26]. Different expression of enzymes necessary for drug metabolism may also be responsible for these differences [26–28]. We have reported the pharmacokinetics of morphine including morphine clearance previously [11]. Sex was included as a covariate for morphine clearance but was not found to be a major predictor of variability in morphine pharmacokinetics in children [11].

In our study, opioid related adverse effects tended to occur more often in girls when high total morphine dose (>0.3 mg/kg) was administered; while in boys such linear trends in increasing opioid adverse effects with total morphine doses were not observed (Table 3). We hypothesized that hormonal differences between boys and girls could potentially explain the sex differences in opioid adverse effects. To potentially explain the mechanism behind the sex differences in opioid adverse effects, we used common pubertal age in girls as surrogate for different hormonal levels associated with puberty and analyzed three age categories for girls: <8 years (prepuberty), 8–13 years (pubertal age), >13 years (postpuberty). In girls, significant association of total morphine dose was detected with PONV, RD, and prolonged PACU due to PONV and RD; younger girls had significantly more RD and PONV with higher doses of morphine (Table 5). Interestingly, age or OSA incidence (higher frequencies in younger girls and boys) were not associated with girls' sensitivity to morphine dose, when the age and OSA effects were tested in multivariate

models, probably due to small number of girls in each age and total morphine dose categories. As high incidences of opioid adverse effects with the high morphine dose (0.3 mg/kg) are apparent across all three age categories (especially in younger girls), these data are not supportive of hormonally mediated differences in girls. However, as we did not perform Tanner staging, it is possible that our age categorization was not a good metric for puberty stage. Clearly additional studies are warranted to confirm our findings, and explain underlying mechanisms.

It is important to note that our analyses were restricted to a single self-reported white population. As our previous studies have demonstrated that there are differences in the risk of side effects by race [3], it was important to analyze by race. Although, the race, per se is not focus of the study, there was more than 95% correlation between self-reported race and ancestry informative markers in our study. Self-report of race is easier to use as it is readily available to clinicians than genetic markers of ancestral origin. Because of the relatively small number of minority children available for meaningful analysis, we focused our results to white children. It is unclear whether or not these differences would still be seen in non-white populations. Thus, future studies should examine sex effect in other racial groups, possibly need for more aggressive PONV and RD prevention strategies for white girls based on the data.

In conclusion, sex differences for dose related opioid adverse effect risks exist in white children. White girls have higher risk of having opioid related RD and PONV and prolonged stays in PACU due to opioid adverse effects with higher doses of morphine than boys undergoing surgery. This difference was not explained by pubertal age or history suggestive of OSA. When treating pain in children, one should keep in mind that while experiencing similar analgesia to boys, white girls are relatively more sensitive to higher doses of opioids, have higher opioid-related adverse events and stay longer in PACU; hence use of opioid-sparing techniques like nonsteroidal analgesics, dexmedetomidine, regional techniques when applicable and use of opioid agonist–antagonists like nalbuphine may be ways to decrease the incidence of opioid-related adverse-effects in girls. Although all the children received nausea prophylaxis in our study, it may be necessary to pursue more prophylactic measures in girls compared with boys receiving high dose opioids. Also, awareness and effective monitoring for opioid adverse effects may be especially relevant for girls younger than 13 years of age, and one may consider restricting morphine doses to $<0.3$ mg/kg for girls compared with boys undergoing tonsillectomies. Thus, the knowledge gained from this study might help prevent unfavorable clinical and economic perioperative outcomes in children.

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