

[PR2-120] Opioid-related adverse effects in children undergoing surgery: Unequal burden on girls

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Background: Unpredictable inter-individual variability in response to opioids results in inadequate analgesia and opioid-related adverse effects; a portion of this variability is race-related. Although multiple, yet inconsistent studies exist regarding opioid modulation and its relation to gender among adults, the effect of a child's sex on opioid response has not been well studied. The aim of this study is to determine the effects of sex on perioperative opioid-related adverse effects in children undergoing tonsillectomy.

Methods: In this prospective observational study, 275 children between 6 and 15 years of age undergoing outpatient tonsillectomy were recruited. All participants received standard perioperative care with a standard intraoperative dose of morphine. Opioid-related analgesia and safety outcomes were collected, including incidences of respiratory depression (RD); postoperative nausea and vomiting (PONV); and incidence of prolonged stay in the post anesthesia recovery unit (PACU) due to these opioid adverse effects. Continuous variables were compared using t-test or Wilcoxon rank-sum test, categorical variables using Fisher's exact test, and the relationship between morphine dose and outcomes by sex using Spearman correlation coefficients.

Results: This study focused on 219 white boys and girls, given the small sample size of non-white children. As the total dose of morphine requirement increased girls had significantly higher incidence of PONV than boys ($p=0.001$), overall major (RD and PONV) opioid adverse effects ($p=0.032$), prolonged PACU stay due to PONV ($p=0.010$), and prolonged PACU stay due to major opioid adverse effects ($p=0.011$) (Figure 1). Girls who had higher (>0.3 mg/kg) dose of morphine had a 30 minute longer stay in PACU ($p=0.0002$) due to opioid adverse effects when compared to girls who had less morphine. There was also a trend for girls receiving the higher dose toward longer stay compared to boys receiving higher dose of morphine (20 minutes longer, $p=0.09$).

Conclusions: For the first time, this study demonstrates that a child's sex influences morphine's adverse effects. As total morphine doses are increased, white girls have an unequal burden of higher incidences of PONV, respiratory depression and prolonged PACU stay than boys. Younger girls (<8 years) had higher incidences of PONV and RD than older girls indicating a non-hormonal underlying mechanism. Girls had about 5% lower morphine clearance than boys. When managing pain in children, as dose of morphine increases, clinicians need to anticipate potentially higher PONV, more frequent RD and longer PACU stays in girls than boys.

References: Sadhasivam S, et al. *Pediatrics*, May 2012; 129 (5): 832

Figure 1a. Prolonged PACU Stay due to Major Side Effects (Respiratory Depression or PONV)

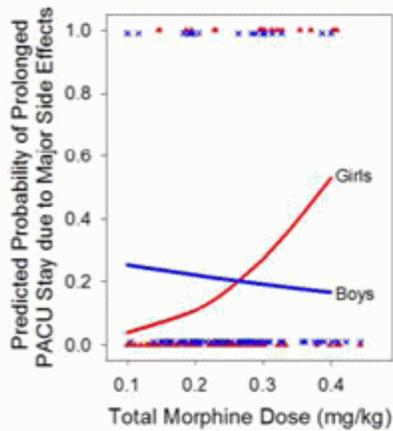


Figure 1b. Sex-specific Differences in Duration of PACU Stay Between Low and High Morphine Doses

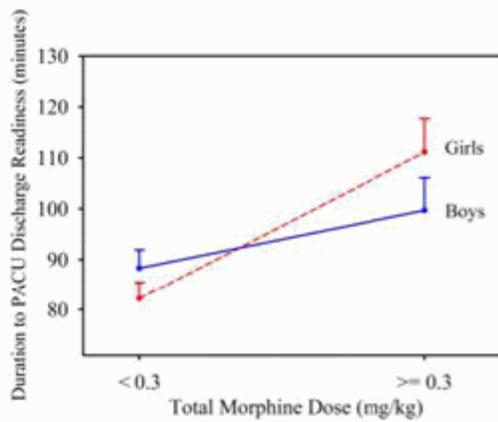


Figure 1. Total morphine dose is plotted along the x axis (1a and 1b). The probability of major opioid related adverse effects leading to prolonged PACU stay as plotted along the y axis in Figure 1a was relatively higher in girls compared with boys as the total morphine dose increased. Figure 1b shows the duration to PACU readiness plotted in y-axis. Girls who had higher (>0.3 mg/kg) dose of morphine had prolonged stay in PACU due to opioid adverse effects than girls who had less morphine (30 minutes longer, $p=0.0002$) and there was a trend towards longer stay compared to boys receiving higher dose of morphine (20 minutes longer, $p=0.09$).