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Commentary on “Letter to the Editor for article titled A Randomized Clinical Trial of the Efficacy of Scheduled Dosing of Acetaminophen and Hydrocodone for the Management of Postoperative Pain in Children After Tonsillectomy”

We thank Drs. Gurnaney and Ganesh for their interest and their comments referring to our recently published article in the February issue of *The Clinical Journal of Pain* (1), and we provide an assessment and discussion of their specific critiques.

First, in response to the comment regarding the trigger for the interim analysis, execution of this study proved to be more difficult than anticipated with a high refusal rate. Data collection had been ongoing for nearly 4 years, and with the funding period close to ending, we needed to close subject enrollment. Only one interim analysis was done which demonstrated a significant difference between the PRN and ATC treatment groups on pain intensity scores, which was the main outcome variable of the study and on which the study was originally powered. We also looked at side effects, but because the side effect differences were more subtle, effect sizes were smaller. The sample size was sufficient to detect medium effect sizes (like we found for pain intensity), but the study was not powered to detect side effect differences with a small effect size. If we had managed to reach the target sample size of 300, the larger sample size wouldn't have necessarily changed the magnitude of the effect sizes, but some of the differences between the 2 groups in the side effects would likely have been statistically significant.

Second, it's suggested that because we excluded the two children in the around-the-clock (ATC) group who were withdrawn from the study early on due to persistent nausea and vomiting, we did not find a significant trend towards increased nausea for children in the ATC group on the third postoperative day. Actually, we reported this exact finding, which was the basis for suggesting in our discussion that scheduled analgesic dosing beyond the first 48 hours after surgery may contribute to an increased potential for this opioid-related side effect.

As Gurnaney and Ganesh point out, a large proportion of children in both treatment groups reported moderate to severe nausea at baseline (i.e., on the first evening after surgery), highlighting the limited duration of effect provided by intraoperative anti-emetic prophylaxis. Patients are rarely discharged home with a prescribed anti-emetic for home use to prevent or treat symptoms as needed. Children should not suffer from pain or nausea and vomiting at home following tonsillectomy, and our findings underscore the need to identify effective management strategies for both. However, rejection of scheduled opioid analgesic dosing, or avoidance of opioids altogether, should not be the approach used to mitigate against the risk for nausea and vomiting.

Third, is the legitimate concern expressed regarding potential risks associated with administration of opioid analgesics in children with obstructive sleep apnea undergoing tonsillectomy. We apologize for the oversight in reporting that the population in our study excluded children with moderate to severe obstructive sleep apnea who were determined by the surgeon to be ineligible for the ambulatory surgery program. It's noteworthy that the majority of children with obstructive sleep apnea who undergo tonsillectomy and adenoidectomy do so with only a clinical diagnosis, and that these children remain susceptible to airway obstruction and all of the problems arising from obstructive sleep apnea for several weeks postoperatively (2). Nevertheless, oral opioid analgesics are routinely prescribed in standard doses for home pain management in children following tonsillectomy. None of the children in our study presented with respiratory complications following discharge home.

Fourth, Gurnaney and Ganesh raise an important point concerning our omission of surgical technique in the reported sample demographics. It was included in our initial manuscript submission, but was subsequently removed at the request of the reviewers to pare down the content to that which we believed the reader would be most interested in seeing. We present additional data on surgical technique for our sample. A large proportion of children had coblation-assisted tonsillectomy. Clinical studies evaluating both intracapsular and total coblation tonsillectomy have reported less postoperative pain compared to surgical techniques (3-6). However, findings from a recent review indicated that there is inadequate evidence to determine whether coblation tonsillectomy is more effective than other methods of tonsillectomy in reducing morbidity, including postoperative pain (7). Regardless, in our study there were no differences between treatment groups suggesting that surgical technique did not account for the significant differences in pain intensity between the PRN and ATC groups.

	PRN Group (n=39) % (n)	ATC Groups Combined (n=74) % (n)	Continuity Corrected χ^2 p-value
Surgical technique – Tonsils			
Blunt dissection	10.3 (4)	9.5 (7)	p = 1.00
Electrocautery	15.4 (6)	13.5 (10)	p = 1.00
Coblation	79.5 (31)	83.8 (62)	p = .76
	(n=39)	(n=74)	
Surgical technique – Adenoids			
Blunt dissection	11.8 (4)	9.4 (6)	p = .98
Electrocautery	88.2 (30)	85.9 (55)	p = 1.00
Coblation	5.9 (2)	21.9 (14)	p = .08

Fifth, in response to the question regarding the triggers in the PRN group to use pain medications, standard teaching did not link analgesic administration to specific pain ratings. Physician written discharge instructions stated, "Give the prescription medications as ordered," and the teaching booklet for children in the PRN group stated, "Give Tylenol with Hydrocodone every 4 hours 'as needed' for pain." No specific instructions were provided to parents regarding behavioral signs of pain, or a specific self-report pain intensity rating that would require analgesic administration. This was consistent with the standard of practice in ambulatory surgery at the children's hospital where the study was conducted.

Finally, we acknowledge that allowing children and their parents to self-select for participation in the study introduces some selection bias. However, all eligible children were approached for participation, randomization eliminated bias in treatment assignment, and there were no systematic differences in the characteristics of those assigned to the PRN or ATC group.

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