In Reply:

I appreciate the constructive comments of Nguyen *et al.* with regard to the recent trial published by Ramgolam *et al.*[1] and the accompanying editorial in Anesthesiology.[2] I certainly agree with the observation that the work station used may have an impact on how long an inhalational induction would take, and this may have an impact on the likelihood of complications during induction; however, in this case it transpires that the researchers did not use a Draeger Primus (Draeger, Germany) for induction but, as is common in Australia, used a separate anesthesia system with a back bar that connected to a T-piece where wash-in times were minimal. This indeed should have been clarified in the paper. Apart from the work station, several other aspects of an inhalational induction may vary between practitioners, such as use of nitrous oxide, fresh gas flow, choice of circuit, and the degree of overpressure used. It is certainly plausible, but not definite, if or how these variations may have an impact on the risk of complications. Nevertheless, variations in practice that could plausibly impact research findings should always be considered when translating trial findings to practice.

Competing Interests

The author declares no competing interests.

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2. Davidson AJ: Induction of anesthesia for children: Should we recommend the needle or the mask? Anesthesiology 2018; 128:1051–2

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In Reply:

We thank our international colleagues for their interest in our study, "Inhalational *versus* Intravenous Induction of Anesthesia in Children with a High Risk of Perioperative Respiratory Adverse Events: A Randomized Controlled Trial,"[1] and have summarized our responses as follows.

Nguyen *et al.* raised the question of complications in the postinduction period and the effect of the route of the induction on complications. It is important to note that our study was neither designed nor powered to address respiratory adverse events within individual anesthesia phases, and data should be interpreted with caution. As demonstrated in table 1, the inhalational group did have the majority of respiratory adverse events during the induction of anesthesia, highlighted by Nguyen *et al.* However, there were no significant differences in the incidence of respiratory adverse events during the other phases of anesthesia. Complications increased across the whole perioperative period (primary outcome measure), as reported in our study.[1] While we cannot specifically comment on the impact on the method of anesthesia induction on complications within each anesthetic phase, we believe the significant reduction of complications within the induction phase and across the perioperative period warrants individual practitioners to give consideration to their clinical practice.

We do agree with Davidson[2] and Nguyen *et al.* that the IV inductions tend to be much faster as compared to inhalational inductions, and that the duration of the induction phase may result in higher complications during that phase and therefore be a mediating factor. In this study, the induction of anesthesia was not performed with the Draeger Primus workstation, which was used throughout the surgery. In our institution, the induction of anesthesia is performed in a separate anesthesia bay using a back bar, which, at the time of the study, had ULCO Engineering - AC30 Systems (ULCO Medical, Australia) connected to a T-piece. While we have not specifically recorded inhalational wash-in times, we would observe that these are minimal using a T-piece and do not feel that potential differences in induction times between IV or inhalation induction will have significantly influenced the incidence of respiratory adverse events in our study.

Daoud raised the issue of the tension between increasing external application of the outcomes and the internal validity of the study. We note that this study was designed in a pragmatic way to improve external validity, and therefore some specific aspects of anesthetic care were not rigidly controlled. One potential impact on complications noted by Daoud was the application of nitrous oxide in the inhalational group and subsequent decreases in oxygenation to less than 95%, which was one of the perioperative complications recorded in this study.[1] In this study, patients undergoing inhalational induction of anesthesia received nitrous oxide at a median ratio (range) of 0.5 (0.5 to 0.66), which is not a large range, particularly given the fact that mask seal is not always perfect during induction in young children. We agree that this means that the inhalational group received a higher F_{IO_2} compared with the IV group, which could possibly have led to an underestimation of the difference between the two techniques, given that preoxygenation was not routine in the IV group, in line with routine practice in many institutions. Our study was not designed nor powered to detect significant differences in individual complications. However, we would note that desaturation was not statistically

Table 1. Rate of Perioperative Respiratory Adverse Events during Each Phase of Anesthesia and over the Perioperative Period (Any Phase of Anesthesia)

Incidence of Respiratory Adverse Events in the Perioperative Period					
Phase	**IV**	**Inhalation**	**Relative Risk**	**95% CI**	***P* Value**
Induction	16 (10.8%)	47 (31.5%)	2.94	1.75–4.94	<0.001
Maintenance	4 (2.7%)	9 (6.0%)	2.25	0.71–7.15	0.26
Emergence	12 (8.1%)	23 (15.4%)	1.92	0.99–3.71	0.071
Recovery	17 (11.4%)	26 (17.4%)	1.53	0.87–2.70	0.19
Any	39 (26.2%)	64 (43.0%)	1.64	1.18–2.28	0.003

IV, intravenous.

different between IV and inhalational induction (26 of 149 [17%] and 38 of 149 [26%]; relative risk, 1.46, 95% CI, 0.94 to 2.28; $P = 0.094$) in our intention-to-treat analysis. We agree with Daoud that a careful comparison of local anesthesia practices and those used in this study will be required by those considering changing their clinical practice to minimize complications in similar patient populations.

Subedi raised the potential impact of patient risk factors (for example, prematurity) and individual variations in clinical practice (such as laryngeal mask airway removal) as potential confounders in this study. We agree there are numerous risk factors that do impact respiratory adverse events. We have previously assessed and reported those risk factors with the largest impact on perioperative respiratory complications in a cohort of more than 9,000 children, and have used the same definitions in this study based on the evidence of our large cohort.[3] These risks factors are reported in our study, are not different between the treatment groups, and therefore had a negligible impact on the outcomes of this study.

While we agree with Deng that preoxygenation is a useful tool in some high-risk patients, the patients studied were relatively well American Society of Anesthesiologists Physical Status I and II patients, even though we studied patients with respiratory risk factors. In line with institutional routine practice, 66% N_2O was used to aid the inhalation induction and preoxygenation was therefore not possible in the inhalational group. To then use preoxygenation in the IV group would have introduced a bias into the trial. However, as previously noted, there were no differences in the number of desaturations across the perioperative period, and we do not feel that this has impacted the outcome of this study.

To further clarify, no patients with an anticipated difficult airway were included. In all patients, the laryngeal mask airway was only inserted after the child did not react to a bimanual jaw thrust maneuver.[4] In line with the pragmatic clinically based trial design, anesthesiologists were free to administer additional propofol in the inhalational group since this is standard practice in many institutions. All patients in the inhalational group who received propofol at the induction of anesthesia received propofol prior to the insertion of the airway device. It is highly unlikely that the patients receiving propofol were in a lighter anesthetic stage than those that did not. In fact, it is more likely that these patients receiving additional propofol were deeper; however, there was no significant difference in respiratory adverse events between the patients of the inhalational group who received propofol prior to airway management and those who did not. We do agree with Daoud, and this is explicitly highlighted in the manuscript, that this analysis is underpowered. This *post hoc* analysis was neither part of our clinical trial protocol nor the trial analytical plan, but was requested as part of the review process by Anesthesiology. Again, the usage of a clinical endpoint to judge the depth of anesthesia before airway management was pragmatic and based on clinical judgment as per routine practice in most institutions. The bimanual jaw thrust maneuver is commonly used for this purpose.

With regards to the results in infants, we only have one child under 1 yr of age in the age group 0 to 3 yr; therefore, a separate analysis is not valid. Similarly, with only a small group of patients receiving caudal blocks, a subgroup analysis, as suggested by Subedi, is not sufficiently powered to perform.

Opioid usage was similar between the groups, with 93% of children in the IV group and 92% of children in the inhalational group receiving opioids. Fentanyl was the most commonly used agent (IV *vs.* inhalational group: 86% *vs.* 84%, respectively), followed by morphine (4% *vs.* 5.5%), pethidine (1% *vs.* 2%), and alfentanil (2% *vs.* 1%). This demonstrates that a bias due to differences in opioid use is unlikely.

Our study was designed with sufficient power to investigate the difference between inhalational and IV induction of anesthesia with regards to the occurrence of respiratory adverse events; however, the study was not designed to investigate any potential interaction effects of sevoflurane and propofol. This would need to be assessed in larger trial settings.

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Competing Interests

The authors declare no competing interests.

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Opiates and IV Acetaminophen

To the Editor:

I read with keen interest the article by Wasserman *et al.*,[1] "Impact of Intravenous Acetaminophen on Perioperative Opioid Utilization and Outcomes in Open Colectomies," in the July issue of Anesthesiology. Using billing codes to determine opiate use in 602 disparate hospitals in various states without knowing precisely what protocols are used renders the conclusion that IV acetaminophen has no important impact on postoperative opioid use in question. Hospitals with excellent compliance with Enhanced Recovery After Surgery Group protocols obtain decreases in opiate use. However, compliance with Enhanced Recovery After Surgery protocols is highly variable from hospital to hospital, let alone from practitioner to practitioner. For instance, some physicians routinely give patients an opiate patient-controlled analgesia in addition to IV acetaminophen as part of a multimodal protocol when they assume a patient is going to have very high demands *versus* oral for those they assume will not. If nursing staff receive scheduled orders for nonsteroidal antiinflammatory drugs or IV acetaminophen but do not deliver them in a timely fashion, the patient may get behind in pain control, thus necessitating rescue opiate. In states with high rates of chronic opiate users, the results will skew to no impact for IV acetaminophen. For that matter, if a patient is given an opiate patient-controlled analgesia but does not use it, the billing codes will still reflect opiate given, when in fact, the patient may not have used it. In hospitals where thoracic epidurals are not routinely used, or if individual patients decline or cannot receive thoracic epidural, opiates become the mainstay treatment for severe pain. Patients who are content with oral acetaminophen are more likely to have either high pain tolerance or negative personal convictions about taking opiates. Those with low tolerance or already taking chronic opiates will likely require potent opiates postoperatively.

Without actually examining doses and types of opiates used, analysis of impact is specious. A person receiving one hydrocodone or a small dose of meperidine for postoperative shivering will display an opiate given, but that cannot be compared with a patient who requires a patient-controlled analgesia. Respiratory events are common after open colectomies in the elderly and in those who smoke and may not always relate to opiates. Ileus is associated with longer surgical or anesthesia times, lack of low thoracic epidural use, prolonged use of nasogastric tubes, and extensive bowel manipulation, not just opiate use.[2] Giving a single dose of IV acetaminophen and expecting a miraculous change in opiate use is unsophisticated at best. IV acetaminophen is a tool like any other in our armamentarium. If we use a tool ineffectively, then we are the problem—not the tool. Avoiding opiates altogether with a robust Enhanced Recovery After Surgery program including IV acetaminophen for 24 h has shown large effects on outcomes.[3] Finally, one has to examine the motivation of Premier Healthcare Solutions, Inc., because their motto is to provide "better care and outcomes at a lower cost." If the driving desire to