Title of Study or Project:	Racial differences in induction times in pediatric anesthesia practice: A retrospective cohort study from the Multicenter Perioperative Outcomes Group Research Consortium
Primary Institution:	Massachusetts General Hospital
Principal Investigator:	Julia M. Rosenbloom, MD
Co-Investigators:	Sara M. Burns MS, David A. August MD PhD, Erik S. Shank MD, Kiara Alvarez PhD, Margarita Alegria PhD, Timothy T Houle PhD
Type of Study:	☐ Exploratory x Retrospective Observational ☐ Prospective Randomized
IRB Number/Status:	Partners IRB approval has been obtained for use of MPOG data (2009P002161/PHS).
Hypothesis:	In three cohorts of pediatric patients, nonwhite children have longer induction times than white children.
Number of Patients/Participants:	The MPOG database will be queried for three cohorts of patients undergoing surgery from January 1, 2010 to present: Cohort 1: children aged 3-17 years old, ASA 1-2, undergoing routine procedures Cohort 2: neonates and infants aged 0-11 months, ASA 1-3, undergoing routine procedures Cohort 3: children aged 3-17, ASA 1-5, undergoing complex surgery (cardiac, neurosurgical, thoracic).
Power Analysis:	Needed sample size: 3,413 The power calculation is based on Cohort 2 since neonates/infants is expected to yield the smallest number of patients for analysis. This power analysis is based on the primary outcome of interest using a multivariable linear regression model with 10 predictors, two-sided alpha=0.05 and 90% power. Further details below.
Proposed statistical test/analysis:	The primary outcome of interest is induction time (minutes) with the exposure of interest being race (aggregated groups of white/nonwhite). Bivariate analysis of the primary outcome and exposure variable will be conducted with a Wilcoxon Rank Sum Test. A generalized linear mixed model with the appropriate link will be utilized to adjust for covariates (including patient demographics, anesthesia/procedure-related factors, and institutional characteristics). Three planned sensitivity analyses include a propensity

	matched analysis, an analysis incorporating multiple imputation for missing data, and an analysis of de-aggregated racial groups (white non-Hispanic, black non-Hispanic, Hispanic, Asian).
Resources (Brief summary of resources for data collection, personnel, financial):	The MPOG database will be queried for the specified Concept IDs. Statistical support and operational oversight will be funded by the Department of Anesthesia, Critical Care, and Pain Medicine at Massachusetts General Hospital.

Introduction

What is the significance of the clinical problem being addressed?

Racial/ethnic disparities in medicine are well-described phenomena that may manifest in lower quality of care and an increase in adverse health outcomes.[1] Salient to our own specialty, for example, studies of surgical populations have demonstrated that black patients have higher rates of morbidity and mortality after orthopedic and oncologic surgeries and have longer operative times for hip, knee, colorectal, and thoracic surgeries.[2,3,4] A small, but growing body of literature has been examining the existence and manifestations of racial/ethnic health service disparities in anesthetic care for adults, such as differences in the rates of regional techniques for hernia repairs and in the use of labor epidurals.[5,6] As yet, only five studies have considered racial/ethnic disparities in pediatric anesthetic care.

What current gaps exist in the understanding of this problem?

Literature on racial/ethnic disparities in pediatric anesthetic care has yielded conflicting results. In 2010, Jimenez and colleagues studied medication administration for pediatric patients undergoing tonsillectomies and adenoidectomies: Latino children were equally likely to receive intraoperative analgesics as whites, but more likely to receive shorter-acting opioids and less likely to receive postoperative opioid medications.[7] A 2012 study focused on care in the PACU and noted that after routine tonsillectomy and adenoidectomy, black children reported higher postoperative pain and required more pain medications, which the authors interpret as a manifestation of significant inter-individual and inter-racial variability in opioid requirements.[8] Rosenbloom et al.'s 2017 study of laparoscopic appendectomies found no significant differences in medication administration to black versus white patients and no difference in the first or highest pain score between racial groups when accounting for patient age, patient gender, and attending anesthesiologist.[9] Nafiu and colleagues demonstrated that receipt of analgesia for acute postoperative pain following elective outpatient surgery was not significantly associated with minority status, although minority children were more likely to receive IV opioids than white children.[10] Most recently, a study of 74 pediatric patients undergoing scoliosis

correction by a single surgeon demonstrated that black children had higher intraoperative blood loss and were more likely to receive intraoperative blood transfusions than white children.[11] Of note, all five studies had small sample sizes and used single-institution data, four of which were from tertiary children's centers: the results may therefore not be representative of care that children receive nationwide. In addition, there was limited attention either to aspects of anesthesia care beyond analgesia in these studies or to patient populations other than healthy children. We need additional studies—with large numbers of subjects and across multiple institutions—because few studies of racial/ethnic disparities in pediatric anesthetic care exist, and the existing ones have limited generalizability and have yielded conflicting results. Millions of children require anesthetics every year in the United States:[12] ensuring quality care and minimal exposure to risk for all children is of significant interest for providers and families.

How will this project address this gap and advance clinical care and/or research knowledge?

We propose to assess for the presence of racial/ethnic disparities in induction time for several reasons. First, our primary outcome reflects the concern of many parents about their child's exposure to anesthetics, especially heightened given the recent statement from the Food and Drug Administration about the potential adverse neurological effects of general anesthetics for children under 3 years: pediatric anesthesiologists must address this topic in most preoperative evaluations.[13] Secondly, there is very little literature or guidelines about induction times in pediatric anesthesia, and previous research has demonstrated that disparities often exists in the setting of individual discretion.[14,15] And finally, induction (and emergence) times have been the focus of literature on disparities in adult anesthesia. In 2013, Silber and colleagues investigated differences in operative time among black and white Medicare patients and found no contribution from anesthesia to this difference.[4]

Based on previous literature, we elect to examine three cohorts of pediatric patients. In order to echo the samples of the three studies on racial/ethnic disparities in pediatric anesthesia, the first cohort focuses on healthy children, undergoing general surgical, otological, and orthopedic procedures.[7,8,9,10]

The second cohort examines neonates and infants given well-documented evidence of racial/ethnic disparities among neonates and infants in the United States, including a much higher rate of death for black and Latino babies.[16,17] And the final cohort includes children undergoing complex procedures (determined by anesthesia CPT codes).[18,19] We hypothesize that nonwhite children in all three cohorts are more likely to have longer induction times than white children. If disparities are found, future work would focus on identifying underlying mechanisms and their clinical implications. Such work might include focus groups, vignettes, or observation in the operating room.

Methods

IRB statement

IRB approval has been obtained for MPOG and written informed consent will be waived.

Study type

Observational (retrospective cohort study). We have referenced the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines and our proposal is in accordance with the checklist.

Primary exposure

We will analyze aggregated groups of white and minority, given likely small sample sizes of each nonwhite group.

Primary outcome

The primary outcome of our study is induction time (in minutes). This will be defined as elapsed time from ‘Patient in Room’ to ‘Induction End Time.’

Secondary outcome(s), where applicable

The secondary outcomes of interest are: a) emergence times in minutes (calculated from ‘Procedure End Time’ to ‘Patient Out of the Room Time’; b) number of intubation attempts (for those cases in which an intubation is performed); c) time under anesthesia in minutes (calculated from ‘Patient in Room’ to

'Patient Out of the Room Time'). The former two secondary outcomes reflect other significant aspects of "anesthesia time"; the latter reflects the total time under anesthesia.

Patient inclusion criteria

Cohort 1: Hernia repairs, closed repairs of upper or lower extremity fractures, ear surgeries, or appendectomies under general anesthesia for 3-17 year old children, American Society of Anesthesiologists Physical Status Classification 1-2.

Cohort 2: Hernia repairs, cleft lip/palate repairs, bronchoscopies, pyloromyotomies, body castings, urological procedures, or noninvasive imaging procedures under general anesthesia for neonates and infants aged 0-11 months, American Society of Anesthesiologists Physical Status Classification 1-3.

Cohort 3: Complex cardiac, thoracic, spine or neurosurgical cases under general anesthesia for 3-17 year old children, American Society of Anesthesiologists Physical Status Classification 1-5.

*Cases to be included were chosen based on literature of pediatric procedures[20,21] and on clinical expertise of research team (JMR, ESS, DAA), including two senior pediatric anesthesiologists who have been in practice for over 20 years (ESS, DAA).

* To be considered for analysis, sites must contribute at least 20 cases.

Patient exclusion criteria

Cohort 1: Emergent cases, those that involve neuraxial or other types of blocks (solely or in addition to general anesthesia) will be excluded. Cases for patients with known difficult airways will also be excluded (Known difficult airway will be determined by preoperative airway assessment and plan).

Cohort 2: Emergent cases, those that involve neuraxial or other types of blocks (solely or in addition to general anesthesia) will be excluded. Cases for patients with known difficult airways will also be excluded (Known difficult airway will be determined by preoperative airway assessment and plan).

Cohort 3: Cases that involve neuraxial or other types of blocks (solely or in addition to general anesthesia) will be excluded. Cases with the use of an LMA will be excluded. Cases for patients with known difficult airways will also be excluded.

*All cases performed in non-US hospitals will be excluded, given that the construct of race in the United States has its own peculiar history and contemporary social, economic, and political consequences.
*Any reason for censoring (such as rare cases of death during induction or malignant hyperthermia) will be excluded so that all cases will be completely observed.

Data source

MPOG database

Statistical analysis

The primary outcome of interest is induction time (minutes). To ensure a consistent definition of induction time, it will be calculated from 'Patient in Room' to 'Induction End Time.' Our unit of analysis is a case; for patients with multiple surgeries, we will use only the index case (first case in the observation period). The primary model will use cases with complete data.

Given that time-to-event data can be skewed, normality will be assessed using Shapiro-Wilk test and a Q-Q plot. To test the primary hypothesis that nonwhites are more likely to have longer induction times than whites, an independent two-sample t-test or Wilcoxon Rank Sum Test will be utilized, as appropriate.

To isolate the impact of the exposure of race on the primary outcome, we will conduct a multivariable model. We will closely examine model fit and assumptions with the plan to perform a three-staged multivariable generalized linear mixed model with the appropriate link. For example, if the data is highly skewed, the model will be built using the log-link function. The model will include fixed effects for covariates and a random effect for hospital site throughout all stages. Distribution of random effects will be evaluated using caterpillar plots, histograms, and descriptive statistics.

In the first stage, we will adjust for patient demographics (race; sex; age; body mass index; presence of respiratory comorbidities such as asthma, upper respiratory infection or sleep apnea; and American Society of Anesthesiologists Physical Status Classification). In the second stage, we will add procedure related covariates (type of induction; procedure); In the final stage, we will add hospital characteristics (geographic location, type of institution).

Sex, presence of respiratory comorbidities, type of induction, and presence of respiratory comorbidities will be coded as binary (male/female, yes/no, and inhalational/intravenous respectively, and yes/no respectively); age and BMI will be coded as continuous variables; American Society of Anesthesiologists Physical Status Classification, geographic location, procedure, and type of institution as categorical. Model calibration will be assessed through a reliability plot, which will analyze the distance between the observed and predicted outcomes.

We will also include three planned sensitivity analyses. In the first, we will use propensity matching to confirm the findings in our primary model. In the second sensitivity analyses, we will use multiple imputation in order to account for missing data. In the third, we will analyze four separate racial/ethnic groups (white non-Hispanic, black non-Hispanic, Hispanic, Asian) for trends.

The secondary outcomes of interest are: a) emergence times in minutes (calculated from 'Procedure End Time' to 'Patient Out of the Room Time'; b) number of intubation attempts for those cases in which an intubation is performed; c) time under anesthesia in minutes (calculated from 'Patient in Room' to 'Patient Out of the Room Time').

To test the hypothesis that nonwhites have longer emergence times, more intubation attempts and longer time under anesthesia, an independent t-test or Wilcoxon Rank Sum Test will be utilized as appropriate. As with the primary outcome, we will run a three-staged multivariable generalized linear mixed model with the appropriate link. The model will include fixed effects for covariates and a random effect for hospital site throughout all stages, mirroring the primary analysis.

All hypothesis testing will be two-tailed with significance interpreted as $p<0.05$.

Power analysis

There is little consistent data about standard induction times in pediatric anesthesia. Published literature suggests inhalation induction times (from mask to intubation) are around 4 minutes for children 6 months to 6 years: (222.8 seconds ±23.80).[22] At our own institution, induction times (from anesthesia start to induction complete) average 13.3 minutes (±6.4) for 3-17 year old patients (range: 3 to 57 minutes) and 22.8 minutes (±14.41) for neonates and infants (range 7 to 84 minutes).

We will power our study using data from our institution. Using available data and the clinical expertise of the research team, we believe a 5-minute difference is significant deviation for both groups. The power calculation is based on the primary outcome of interest for Cohort 2 since neonates/infants are expected to yield the smallest number of patients for analysis. With an ICC of 0.1 and 20 clusters, a sample size of 3,413 will allow us to detect a clinically meaningful difference of 5 minutes or greater (partial R^2=0.014) between the two racial/ethnic groups. Group sizes are assumed to be equal (1706/group) and the standard deviation is assumed to be 14.4 minutes. This power analysis was constructed for a multivariable linear regression model with 10 predictors, two-sided alpha=0.05 and 90% power.

Variables to be collected

Source	Data Column	ID	
Races and Ethnicities (Exposure)	Race	4000-4009	
Intraoperative Events, Interventions, and Observations (Outcome 1)	AACD Patient in Room Date/Time	50003	
Intraoperative Events, Interventions, and Observations (Outcome 1)	AACD Induction End Date/Time	50005	
Intraoperative Events,	AACD Procedure Finish Date/Time	50007	

Interventions, and Observations (Outcome 2)			
Intraoperative Events, Interventions, and Observations (Outcome 2)	AACD Patient Out of Room Date/Time	50008	
Intraoperative Events, Interventions, and Observations (Outcome 2)	Intubation-Number of Attempts	50118	
Demographics (covariate-group 1)	Sex		
Preoperative Observations (covariate-group 1)	Physical Exam-Age	70250	
Preoperative Observations (covariate-group 1)	Physical Exam-Body Mass Index	70253	
Preoperative Observations (covariate-group 1)	Respiratory-Upper Resp Infection	70124	
Preoperative Observations (covariate-group 1)	Respiratory-Sleep Apnea	70122	
Preoperative Observations (covariate-group 1)	Assessment and Plan-ASA Physical Status	70233	
Intraoperative Events, Interventions, and Observations (covariate-group 2)	Induction-GA Induction type (mask, iv, rapid)	50311	
Case Type (covariate-group 2)	Primary Anesthesia CPT		
Case Type (covariate-group 2)	Primary surgery CPT Code		
General case information (covariate-group 3)	Institution—de-identified code		
Institution region (covariate)	Institution region		Using US Census regions (Northeast, South, Midwest, West)
Institution type (covariate)	Institution type		University-affiliated vs. non-university affiliated
Preoperative Observations (exclusion criteria)	Assessment and Plan-Airway Plan	70416	

Outcome Observations (exclusion criteria)	Malignant Hyperthermia	90204	
Outcome Observations (exclusion criteria)	Death	90311	

Handling of missing data

To address the problem of missing data, we will use multiple imputation in a sensitivity analysis. Our primary model will include only cases with complete data (to include exposure, outcome, and covariates).

Areas for discussion/known limitations

- Unknown clinical scenario (common problem with observational studies)
- Missing race data and possible selection bias
- Time measurement: use of algorithm, centers with time stamps only

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