Anesthesiology in 2023: Articles You Need to Know

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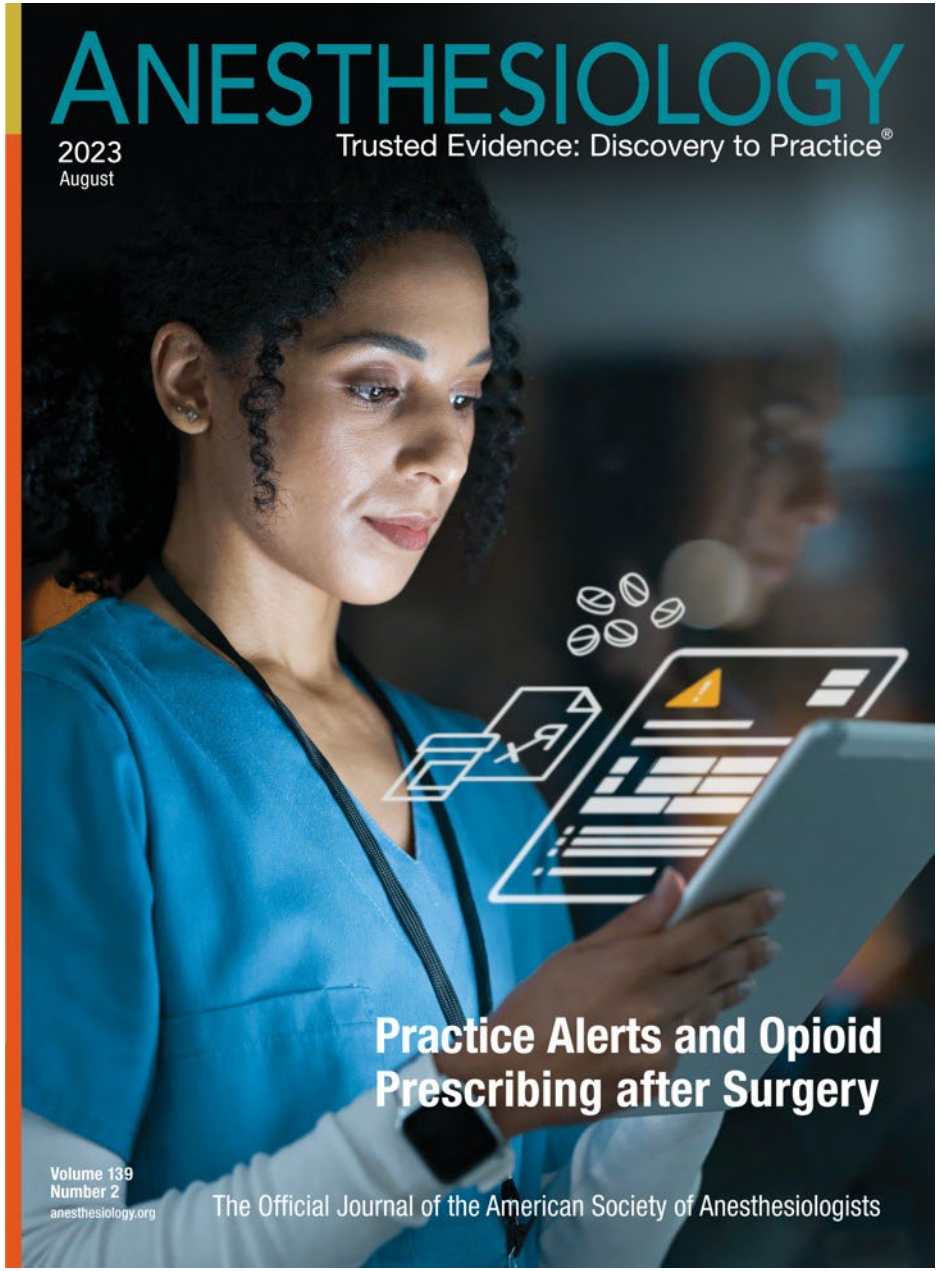
PERIOPERATIVE MEDICINE

ANESTHESIOLOGY

Attributable Perioperative Cost of Frailty after Major, Elective Noncardiac Surgery: A Population-based Cohort Study

Ryan McGinn, M.D., M.Sc., Yonathan Agung, M.Sc., Alexa L. Grudzinski, M.D., Robert Talarico, M.Sc., Julie Hallet, M.D., M.Sc., Daniel I. McIsaac, M.D., M.P.H.

ANESTHESIOLOGY 2023; 139:143–52



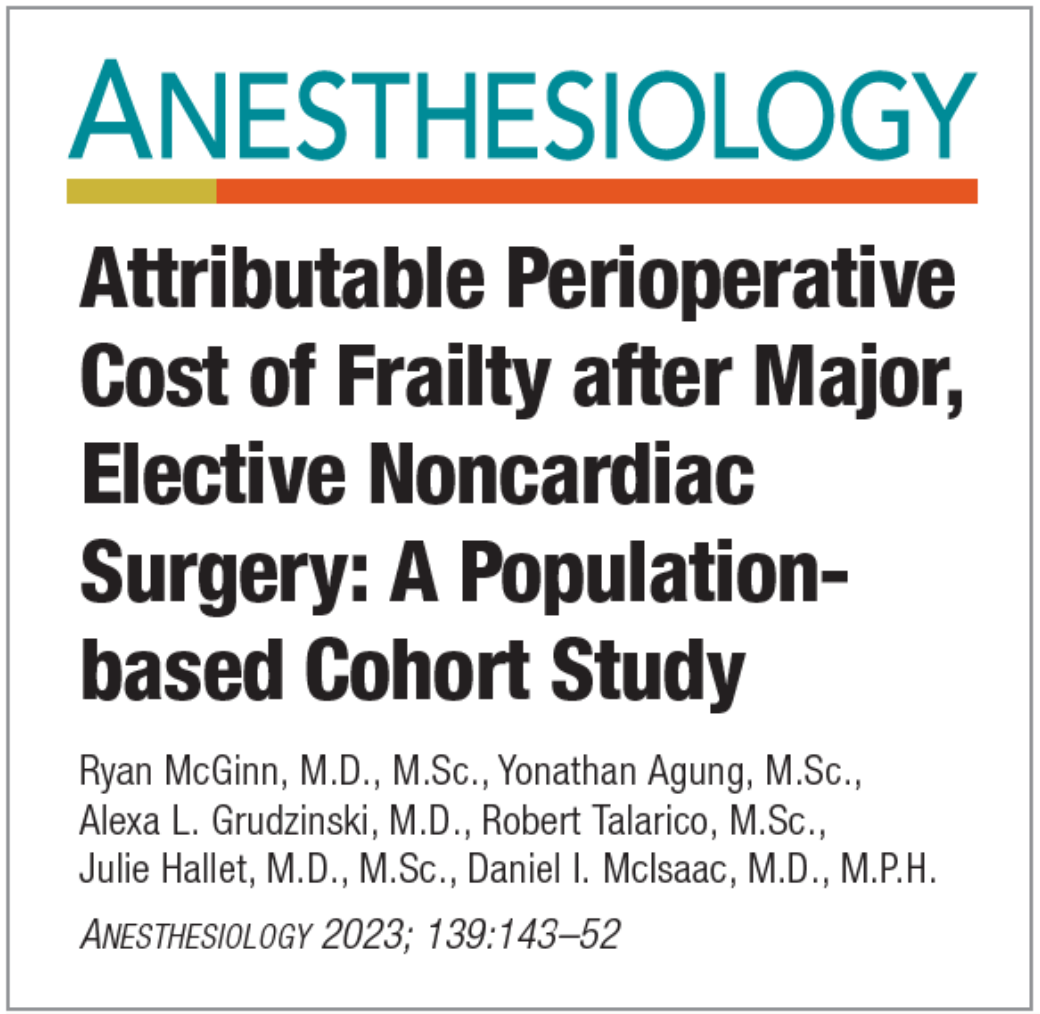
EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients with frailty experience higher rates of perioperative mortality and morbidity
- The extent to which patients with frailty demonstrate higher costs in the year after surgery remains unclear

What This Article Tells Us That Is New

- In a linked administrative dataset of 171,576 patients age 66 yr or older undergoing elective, noncardiac surgery in Ontario between 2012 and 2018, 23,219 (13.5%) demonstrated frailty defined using a multidimensional frailty index
- After adjusting for confounders, patients with frailty demonstrated an absolute cost increase of $11,828 Canadian dollar (ratio of means 1.53; 95% CI, 1.51 to 1.56)
- Among the various components of total 1-yr costs, postacute care costs had the largest relative increase



Rationale

- Patients with frailty consistently experience more perioperative morbidity and mortality
- Costs attributable to frailty remain poorly defined
- This study used a validated frailty index to identify frailty
- Estimated the attributable costs of frailty in the year after major, elective noncardiac surgery.

Methods:

- Retrospective population-based cohort study
- ALL patients 66 yr or older having major, elective noncardiac surgery between 4/1/2012, and 3/31/2018
- Health data obtained from an independent research institute (ICES) in Ontario, Canada
- Preoperative frailty determined using a multidimensional frailty index
- Primary outcome: total health system costs in the year after surgery

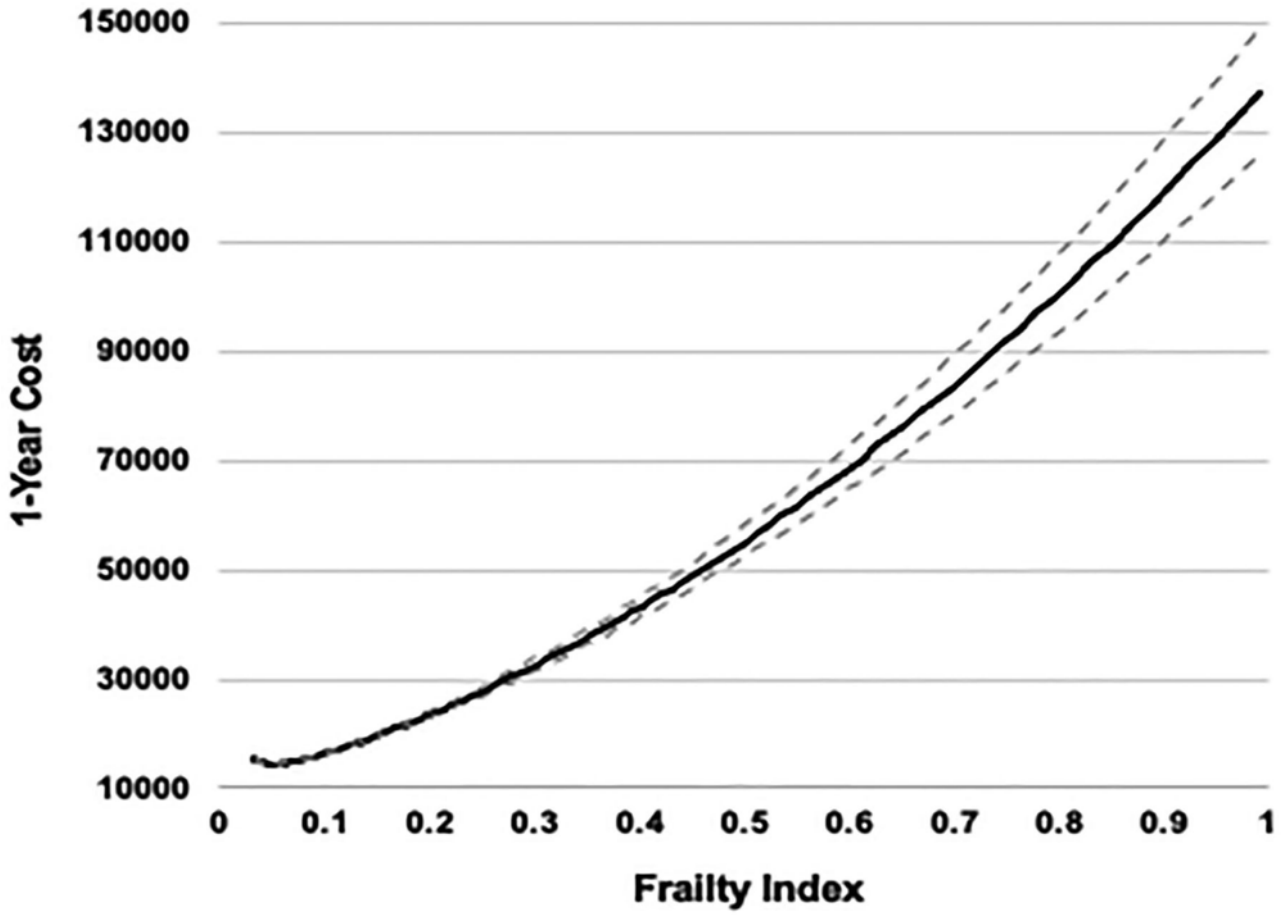
Results

Table 2. Total Perioperative and Component Costs at 1 yr by Frailty Status

Costs	Frailty		Absolute Standard Difference
	No	Yes	
Total costs	26,559 ± 26,151	52,434 ± 50,448	0.64
Hospital costs	15,928 ± 17,281	29,371 ± 36,688	0.47
Postacute care costs	2,502 ± 7,790	7,945 ± 16,452	0.42
Physician billing	5,037 ± 3,450	8,228 ± 5,490	0.70
Other costs	3,092 ± 7,182	6,889 ± 12,238	0.38

Hospital costs include inpatient surgeries and hospital admissions, as well as same-day surgeries after the index procedure). Postacute care costs include rehabilitation, complex and continuing care, long-term care, and home care services. Physician billing includes any insured physician service, as well as capitated costs for non–fee-for-service primary care provision. Other costs include prescription medications, cancer care, dialysis, and emergency department visits.[28] All costs are expressed in 2018 Canadian dollars, presented as mean ± SD.

Results



Adjusted association of frailty and 1-yr postoperative costs with frailty parameterized as a continuous, non-linear second-degree fractional polynomial. Dark line represents the mean, with shaded areas representing 95% CI.

Perioperative Cost of Frailty after Major, Elective Noncardiac Surgery

A population-based cohort study

Background:

- Frailty more than doubles the risk of postoperative morbidity, mortality, and loss of independence
- An aging population increases the number of surgical patients with frailty

Primary aim: Estimate the total perioperative costs attributable to frailty in the year after elective, major noncardiac surgery

Frailty was associated with higher costs in the year after surgery

Total perioperative costs at 1 yr by frailty status

	No Frailty	Frailty	ASD
Total costs	CAD$ 26,559 ± 26,151	CAD$ 52,434 ± 50,448	0.64

All costs are expressed in 2018 Canadian dollars, presented as mean ± standard deviation. ASD: absolute standard difference.

Frailty is associated with a significant increase in health system costs during the first postoperative year, leading to hundreds of millions in extra health system spending

McGinn R, *et al.* Anesthesiology, 2023.

ANESTHESIOLOGY

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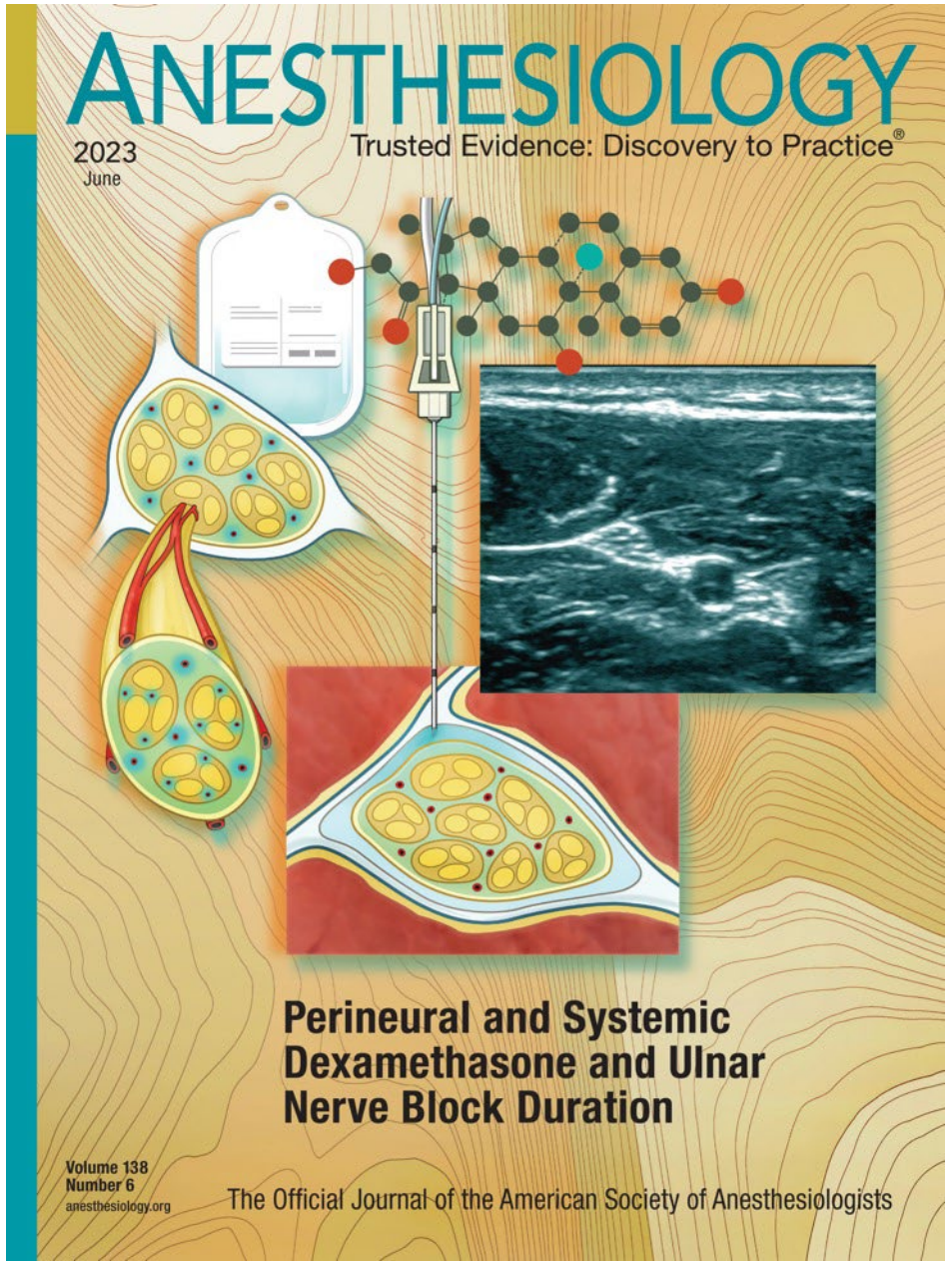
PERIOPERATIVE MEDICINE

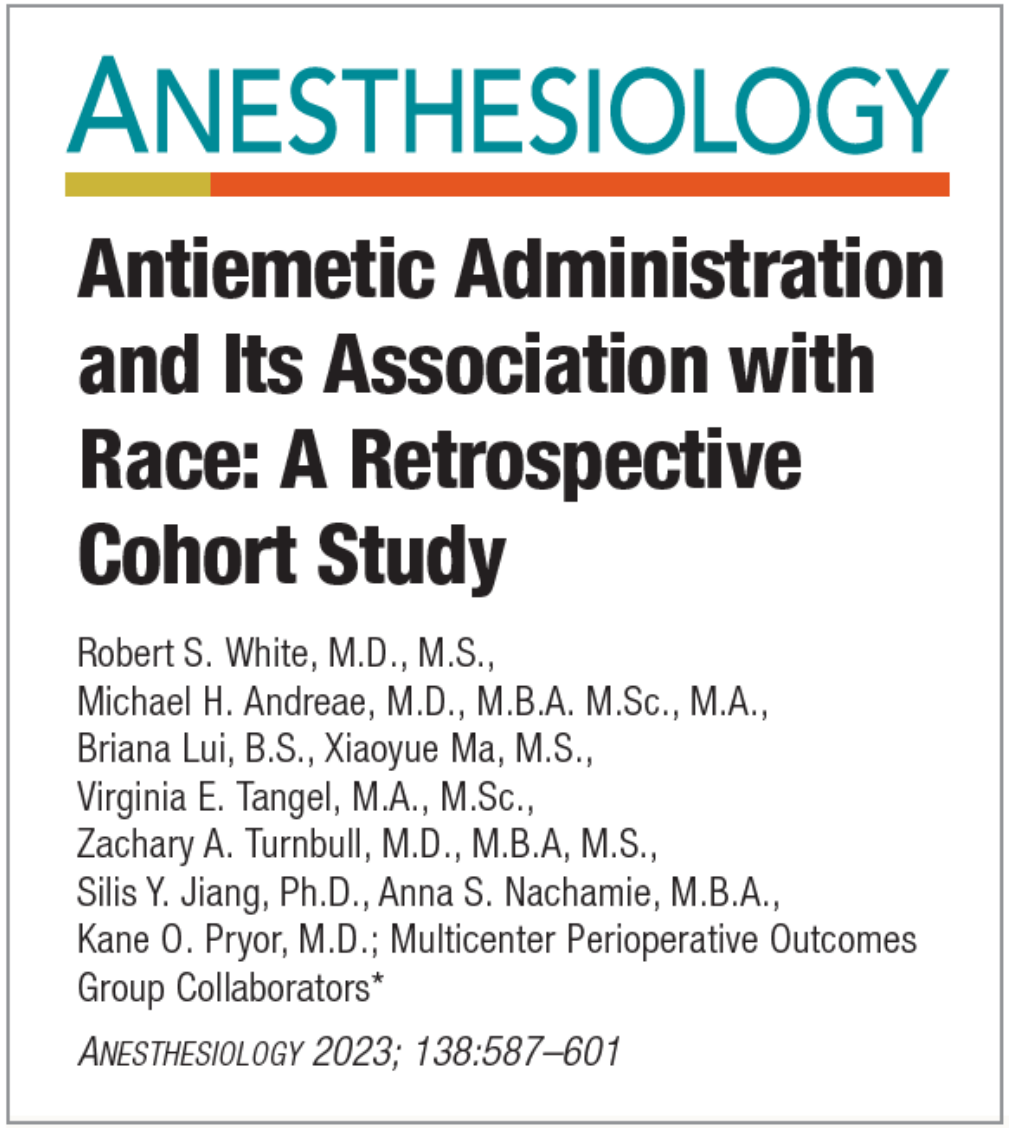
ANESTHESIOLOGY

Antiemetic Administration and Its Association with Race: A Retrospective Cohort Study

Robert S. White, M.D., M.S.,
Michael H. Andreae, M.D., M.B.A. M.Sc., M.A.,
Briana Lui, B.S., Xiaoyue Ma, M.S.,
Virginia E. Tangel, M.A., M.Sc.,
Zachary A. Turnbull, M.D., M.B.A, M.S.,
Silis Y. Jiang, Ph.D., Anna S. Nachamie, M.B.A.,
Kane O. Pryor, M.D.; Multicenter Perioperative Outcomes Group Collaborators*

ANESTHESIOLOGY 2023; 138:587–601





Rationale

- Anesthesiologists' contribution to perioperative healthcare disparities remains unknown
- Postoperative nausea and vomiting is a patient-centered outcome measure
- Antiemetic administration is under the domain of anesthesiologists
- A prior study has demonstrated that Medicaid insured versus commercially insured patients and those with lower versus higher median income had reduced antiemetic administration
- This study tested the hypothesis that black race is associated with lower perioperative antiemetic administration

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Social determinants, such as race, may lead to disparities in health care
- Perioperative antiemetic administration has been found to differ with socioeconomic status

What This Article Tells Us That Is New

- Using data from the Multicenter Perioperative Outcomes Group registry and adjusting for Apfel postoperative nausea and vomiting risk factors, Black *versus* White patient race was associated with less antiemetic administration

Methods:

- 2004 to 2018 MPOG data was used
- Adult patients 18 years of age and older
- Patient race was categorized as either White, Black, other, or unknown
- Primary outcome: administration of either ondansetron or dexamethasone
- Secondary outcomes: administration of each drug individually or both drugs together

Methods (2):

- Confounder-adjusted analysis included relevant patient demographics (postoperative nausea and vomiting risk factors: sex, smoking history, postoperative nausea and vomiting or motion sickness history, and postoperative opioid use)
- Hospital-level variables included American Hospital Association size
- American Hospital Association teaching status
- Multicenter Perioperative Outcomes Group academic center

Methods (3)

- 5,105,123 adult anesthetic records from 39 hospitals in the United States and The Netherlands between 2004 to 2018 were identifies
- After exclusion for exclusion for missing sex, missing ASA status, or ASA Physical Status of 6, 5,000,136 anesthetic records (representing 3,234,312 unique patients were included in the analysis

Outcomes

- Black patients were less likely to receive antiemetic administration with either ondansetron or dexamethasone (adjusted odds ratio, 0.82; 95% CI, 0.81 to 0.82)

Conclusions

- More work is needed to delineate the mechanisms that are driving these and other perioperative disparities in outcomes

Antiemetic Administration and Its Association with Race: A Retrospective Cohort Study

Study of antiemetic administration and patient race in adults using 2004 to 2018 Multicenter Perioperative Outcomes Group (MPOG) data

Primary outcome: Ondansetron or dexamethasone administered

Based on patient risk factors:

Race	Sex	Age	Postoperative opioids
History of smoking or PONV		History of motion sickness	

Analyzed 5.1 million cases from 39 MPOG institutions in the United States and The Netherlands

The Netherlands United States

Black patients (*versus* White patients) were less likely to receive ondansetron or dexamethasone (aOR: 0.82, 95% CI: 0.81-0.82) after adjusting for patient PONV risk factors

In a multicenter perioperative registry data set, Black *versus* White patient race was associated with less antiemetic administration, after controlling for PONV risk factors

White RS, *et al.* Anesthesiology, 2023.

ANESTHESIOLOGY

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"People, We Have a Problem"

Warren S. Sandberg, M.D., Ph.D., Andrew Davidson, M.B.B.S., M.D., F.A.N.Z.C.A., F.A.H.M.S.

The droll line "Houston, we have a problem" by the commander of Apollo 13 announced some troubling observations of unknown significance and impact, and set in motion an urgent but deliberate search for understanding the problem's meaning for the crew, and to engineer solutions. Although the outcome of the Apollo 13 mission is known, the "we have problem" phrase has become a clarion call for focused attention to a perceived problem, its meaning, and a reliable solution in a hurry. In this issue of Anesthesiology, White *et al.* observe in a large retrospective cohort that black patients receive perioperative antiemetic administration at a lower rate than white patients.[1] This result should be

"Practitioners and leaders in the field should reflect on whether there are biases in our practices […]."

realization that the author's institution's performance was included in the contributed data and that the author's own individual performance might have contributed to the observation that anesthesiologists at least seem to treat their patients differently on the basis of race. Revulsion at the potential evidence of wholesale self-deception despite our pious profession of objectivity and patient-centeredness. Awe at the development of the tools to perform such important and paradigm-challenging research *via* the Multicenter Perioperative Outcomes Group, hard-fought by its dedicated members since its initial proof-of-concept publication[2] to this extraordinarily provocative one. These emotions are the result of attribution biases, apprehend-

EDITORIAL

"People, We Have a Problem"

Warren S. Sandberg, M.D., Ph.D., Andrew Davidson, M.B.B.S., M.D., F.A.N.Z.C.A., F.A.H.M.S.

"One editorialist remembers distinctly the initial viewing and shock at seeing figure 2 from the paper by White et al., essentially unchanged in its now published form, at the poster discussion session at the 2019 American Society of Anesthesiologists (ASA; Schaumburg, Illinois) meeting in Orlando, Florida. Shame, revulsion, and awe were competing emotions as this editorialist carefully lined up the image in the camera of his smart phone and snapped (several) images to ensure the result would not be lost."

Anesthesiology June 2023, Vol. 138, 581–584.

EDITORIAL

"People, We Have a Problem"

Warren S. Sandberg, M.D., Ph.D., Andrew Davidson, M.B.B.S., M.D., F.A.N.Z.C.A., F.A.H.M.S.

"The uncomfortable counterpoint is that there might be a biologic basis for a link between race and postoperative nausea and vomiting susceptibility and that this biologic basis is implicitly recognized and accounted or by anesthesia care teams. This would mean that the observed treatment is, in fact, appropriately tailored to patient needs, but the information used by the care teams to refine their prophylaxis and treatment decisions is not available in the observational data."

Anesthesiology June 2023, Vol. 138, 581–584.

Correspondence | September 2023

People, We Have a Problem: Comment

Allison J. Lee, M.D., M.S.; Paloma Toledo, M.D., M.P.H.; Andrea T. Deyrup, M.D., Ph.D.; Joseph L. Graves, Jr., Ph.D.; Dolores B. Njoku, M.D.; Jean R. Guglielminotti, M.D., Ph.D.

+ Author and Article Information

Anesthesiology September 2023, Vol. 139, 364–365.

"The authors (of the original article) painstakingly detailed why these findings should not be attributed to biologic differences between socially defined races, and instead, that we as providers need to consider that this disparity is rooted in bias, implicit, or possibly explicit."

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“However, ... in the accompanying editorial they tell us that ‘The uncomfortable counterpoint [to the conclusion that implicit or explicit bias among anesthesiologists led to disparities in antiemetic administration] is that there might be a biologic basis for a link between race and postoperative nausea and vomiting susceptibility and that this biologic basis is implicitly recognized and accounted for by anesthesia care teams…’

Herein lies our greatest concern—the juxtaposition of this flawed assertion alongside descriptions of reactions of shame regarding the study findings, together with a call to action for anesthesiologists to question their own biases and address such disparities.”

Anesthesiology 2023;139:364-365

"Although socially defined race may in some cases serve as a proxy for exposures (e.g., socioeconomic deprivation, exposure to toxins), and hints at geographic ancestry…

…it has been well documented that there is more genetic variability within socially defined races than between them."

Anesthesiology 2023;139:364-365

CRITICAL CARE MEDICINE

ANESTHESIOLOGY

Performance of Noninvasive Airway Occlusion Maneuvers to Assess Lung Stress and Diaphragm Effort in Mechanically Ventilated Critically Ill Patients

Heder J. de Vries, M.D., Pieter R. Tuinman, M.D., Ph.D., Annemijn H. Jonkman, Ph.D., Ling Liu, M.D., Ph.D., Haibo Qiu, M.D., Ph.D., Armand R. J. Girbes, M.D., Ph.D., YingRui Zhang, M.D., Angelique M. E. de Man, M.D., Ph.D., Harm-Jan de Grooth, M.D., Ph.D., Leo Heunks, M.D., Ph.D.

ANESTHESIOLOGY 2023; 138:274–88

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Recent research suggests that optimization of diaphragmatic effort and avoidance of excessive lung stress may facilitate liberation from mechanical ventilation in critically ill patients
- Low diaphragmatic effort has been associated with rapid development of disuse atrophy, and excessive effort may result in muscle injury, increased lung stress, and pendelluft (displaced ventilation from recruited to nonrecruited lung regions)
- Monitoring transdiaphragmatic and transpulmonary pressures may facilitate accurate assessment of diaphragmatic effort and lung stress, respectively, but requires esophageal and gastric manometry, an overly complex process for routine clinical practice

EDITOR'S PERSPECTIVE

What This Article Tells Us That Is New

- A secondary analysis of two previous studies evaluated the ability of two transient inspiratory airway occlusion maneuvers (Pocc, the total drop in airway pressure during an occlusion, and P0.1, the drop in the first 100 ms) obtained from the mechanical ventilator to predict either diaphragm effort or lung stress
- Neither P0.1 nor Pocc should be used to predict exact values for diaphragm effort or lung distending pressure
- However, both maneuvers can reliably identify patients with low or high extremes in diaphragm effort and lung stress, where Pocc outperforms P0.1 based on the areas under the receiver operating characteristic curves

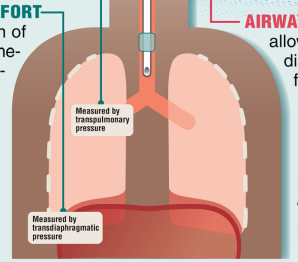
BREATHING EASY

Can Stress & Effort Be Measured Noninvasively in Mechanically Ventilated Patients?

Monitoring and controlling **LUNG STRESS** and **DIAPHRAGM EFFORT** during mechanical ventilation of critically ill patients is likely beneficial to prevent lung and diaphragm injury. This requires esophageal and gastric manometry, which are invasive and complex to interpret.[1]

Lung stress: *high distending pressures can cause barotrauma*

Diaphragm effort: *low effort leads to atrophy, high leads to fatigue*



AIRWAY OCCLUSION MEASUREMENTS allow estimation of lung stress and diaphragm effort without the need for esophageal manometry. Their correlation with and ability to substitute for reference methods is unknown.

P_{occ} = *drop in airway pressure during an inspiration against an occluded airway*

$P_{0.1}$ = *drop in airway pressure in the first 100ms of occluded inspiration*

In this issue of Anesthesiology, de Vries *et al.* investigated whether P_{occ} and $P_{0.1}$ correlate with and can be used to discriminate extremes of lung stress and diaphragm effort, as assessed by esophageal manometry.[2]

	Correlation with observed change in transpulmonary pressure	Correlation with observed change in transdiaphragmatic pressure
P_{occ}	Fair $R^2 = 0.62$ ✓	Fair $R^2 = 0.53$ ✓
$P_{0.1}$	Fair $R^2 = 0.51$ ✓	Poor $R^2 = 0.22$ ✗

	High Lung Stress: Change in transpulmonary pressure >20 cm H_2O	Low Diaphragm Effort: Change in transdiaphragmatic pressure <3 cm H_2O	High Diaphragm Effort: Change in transdiaphragmatic pressure >12 cm H_2O
P_{occ}	Area under the receiver operating characteristic curve **0.90** Accuracy **85%** ✓	Area under the receiver operating characteristic curve **0.97** Accuracy **92%** ✓	Area under the receiver operating characteristic curve **0.86** Accuracy **80%** ✓
$P_{0.1}$	Area under the receiver operating characteristic curve **0.88** Accuracy **81%** ✓	Area under the receiver operating characteristic curve **0.93** Accuracy **89%** ✓	Area under the receiver operating characteristic curve **0.73** Accuracy **71%** ✓

CONCLUSIONS:

P_{occ} and $P_{0.1}$ correlate well with observed change in transpulmonary pressure and observed change in transdiaphragmatic pressure. However, these noninvasive measurements cannot replace esophageal pressure when precise values are required due to wide limits of agreement.

P_{occ} and $P_{0.1}$ have excellent diagnostic performance in identifying high lung stress and low diaphragm effort. P_{occ} is more accurate than $P_{0.1}$ in identifying patients with high diaphragm effort.

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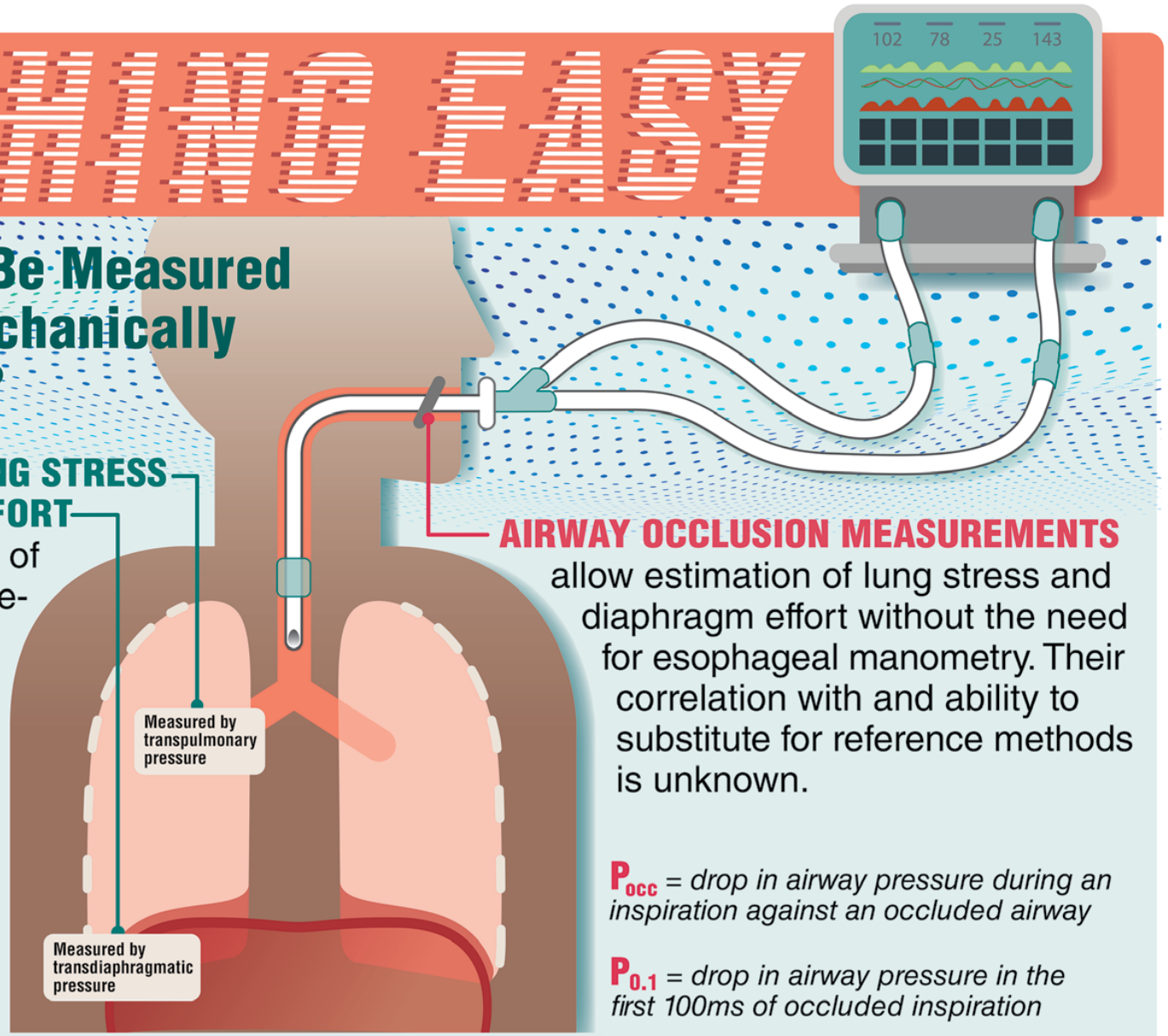

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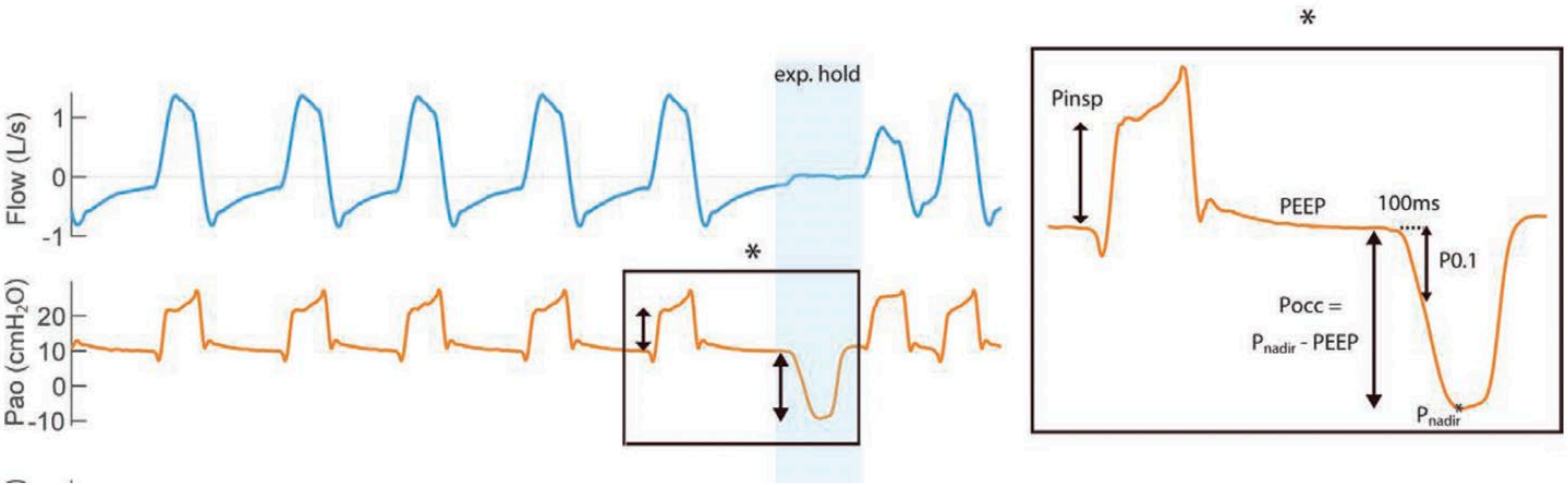
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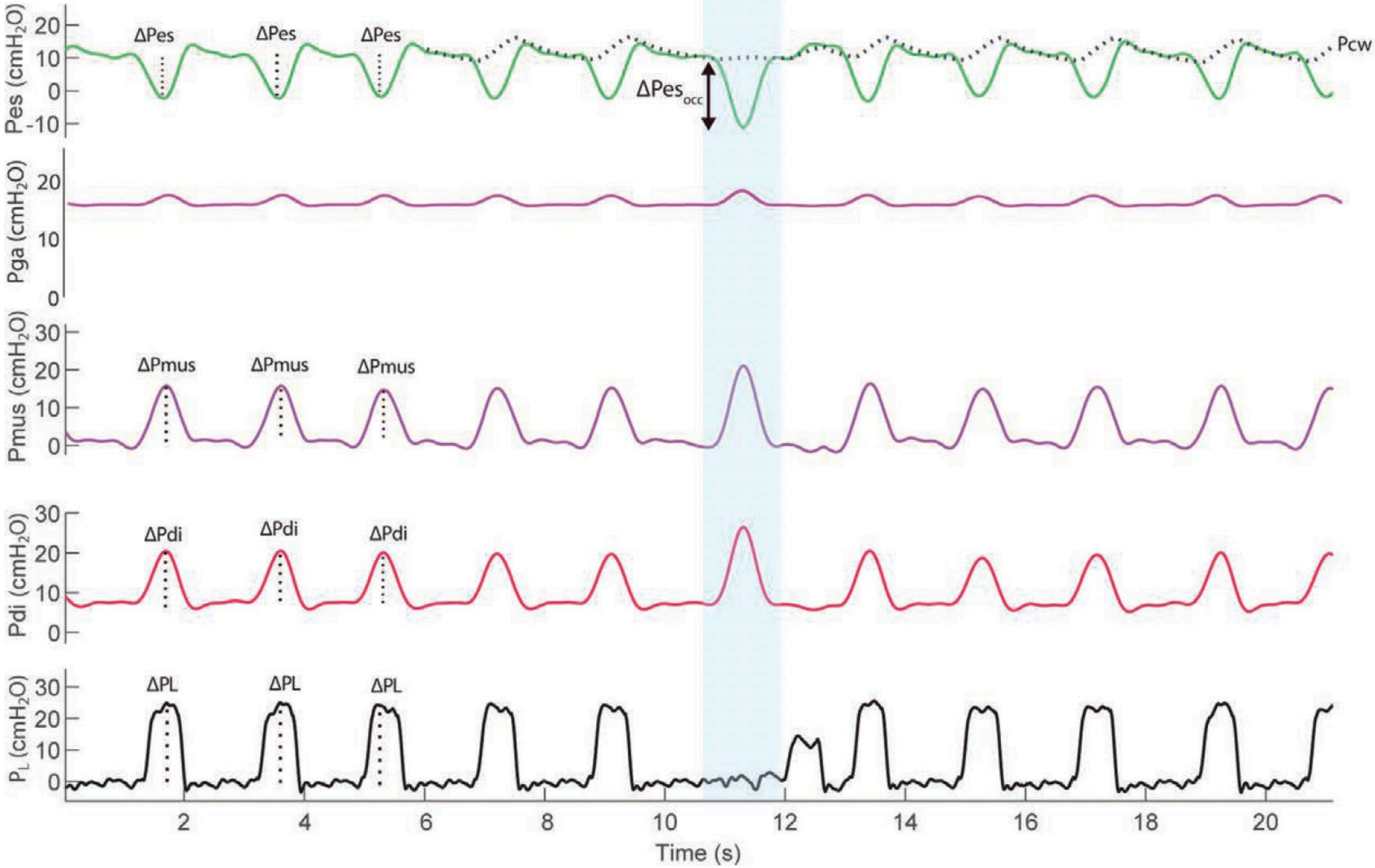
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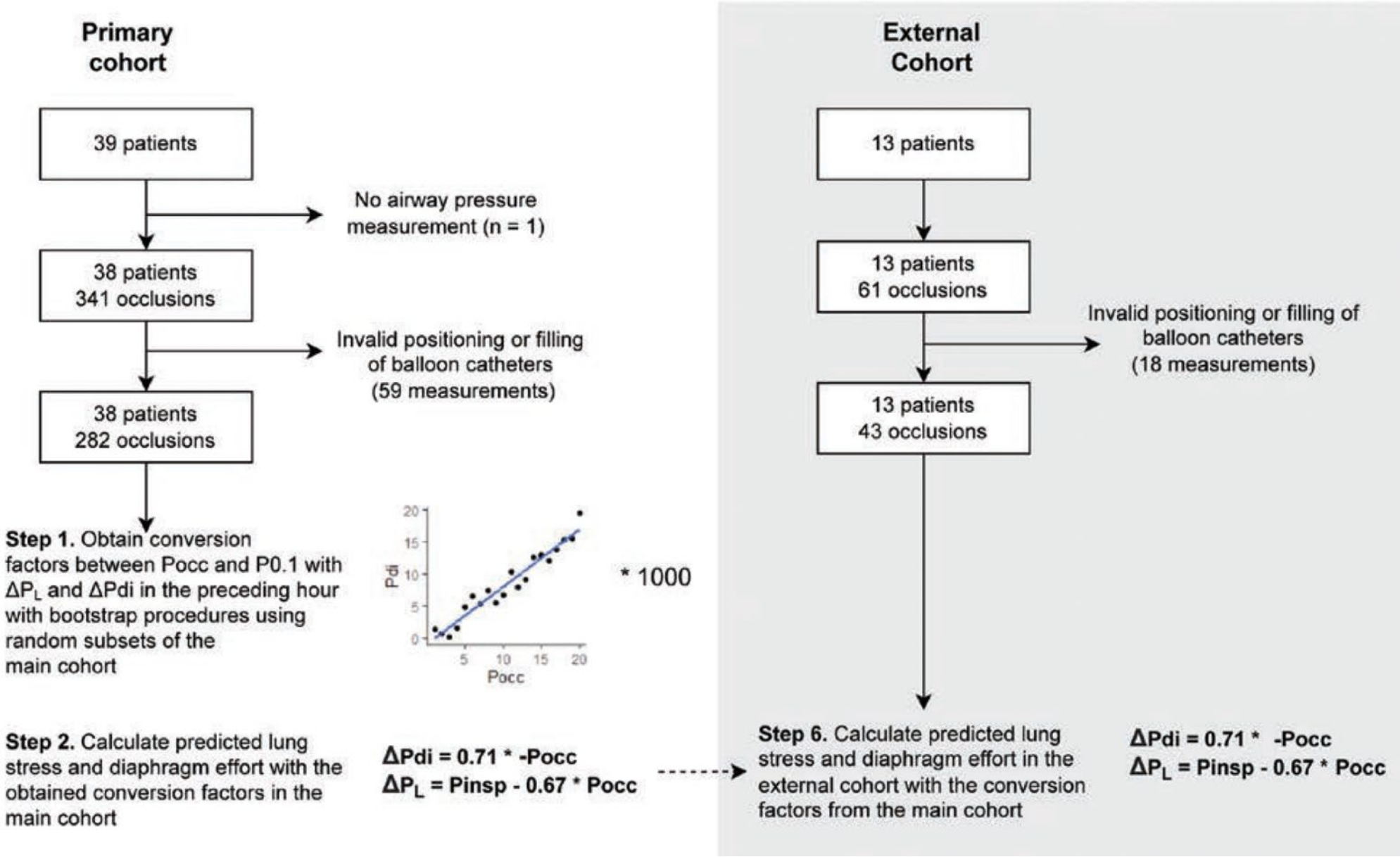
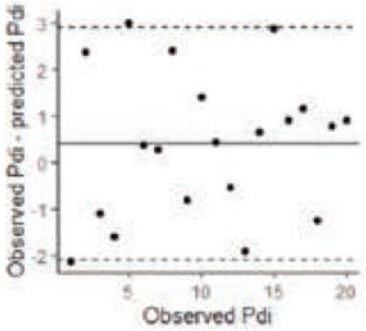
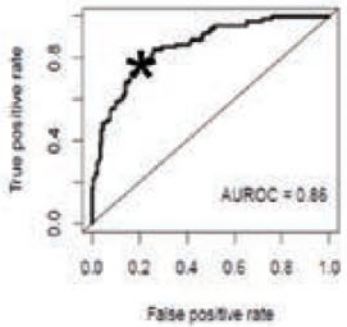

Primary cohort
39 patients
No airway pressure measurement (n = 1)
38 patients
341 occlusions
Invalid positioning or filling of balloon catheters (59 measurements)
38 patients
282 occlusions
Step 1. Obtain conversion factors between Pocc and P0.1 with ΔP_L and ΔPdi in the preceding hour with bootstrap procedures using random subsets of the main cohort
Pdi
Pocc
* 1000
Step 2. Calculate predicted lung stress and diaphragm effort with the obtained conversion factors in the main cohort
ΔPdi = 0.71 * -Pocc
ΔP_L = Pinsp - 0.67 * Pocc
External Cohort
13 patients
13 patients
61 occlusions
Invalid positioning or filling of balloon catheters (18 measurements)
13 patients
43 occlusions
Step 6. Calculate predicted lung stress and diaphragm effort in the external cohort with the conversion factors from the main cohort
ΔPdi = 0.71 * -Pocc
ΔP_L = Pinsp - 0.67 * Pocc

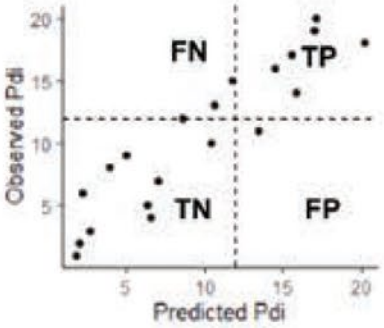
Step 3. Assess accuracy of predicted lung stress and diaphragm effort versus observed lung stress and diaphragm effort in preceding hour with Bland-Altman plots



Step 4. Calculate the area under the receiver-operator characteristic curves (AUROC) and select cut-offs with highest Youden J-statistic

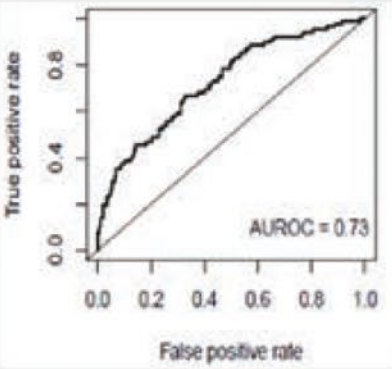


Step 5. Calculate accuracy of the obtained cut-offs in the main cohort by adding true positives (TP) and true negatives (TN), and dividing this sum by the total number of observations including false positives (FP) and false negatives (FN)

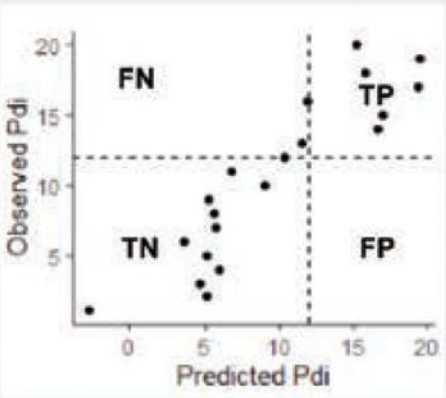


$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN}$$

Step 7. Calculate the area under the receiver-operator characteristic curves (AUROC) with data from external cohort



Step 8. Calculate the accuracy of the index tests with the cut-offs from the main cohort



In this issue of ANESTHESIOLOGY, de Vries *et al.* investigated whether P_{OCC} and $P_{0.1}$ correlate with and can be used to discriminate extremes of lung stress and diaphragm effort, as assessed by esophageal manometry.[2]

	Correlation with observed change in transpulmonary pressure	Correlation with observed change in transdiaphragmatic pressure	High Lung Stress Change in transpulmonary pressure >20 cm H_2O	Low Diaphragm Effort Change in transdiaphragmatic pressure <3 cm H_2O	High Diaphragm Effort Change in transdiaphragmatic pressure >12 cm H_2O
P_{OCC}	Fair $R^2 = 0.62$ ✓	Fair $R^2 = 0.53$ ✓	Area under the receiver operating characteristic curve **0.90** Accuracy **85%** ✓	Area under the receiver operating characteristic curve **0.97** Accuracy **92%** ✓	Area under the receiver operating characteristic curve **0.86** Accuracy **80%** ✓
$P_{0.1}$	Fair $R^2 = 0.51$ ✓	Poor $R^2 = 0.22$ ✗	Area under the receiver operating characteristic curve **0.88** Accuracy **81%** ✓	Area under the receiver operating characteristic curve **0.93** Accuracy **89%** ✓	Area under the receiver operating characteristic curve **0.73** Accuracy **71%** ✓

CONCLUSIONS:

P_{OCC} and $P_{0.1}$ correlate well with observed change in transpulmonary pressure and observed change in transdiaphragmatic pressure. However, these noninvasive measurements cannot replace esophageal pressure when precise values are required due to wide limits of agreement.

P_{OCC} and $P_{0.1}$ have excellent diagnostic performance in identifying high lung stress and low diaphragm effort. P_{OCC} is more accurate than $P_{0.1}$ in identifying patients with high diaphragm effort.

Monitoring Respiratory Effort and Lung-distending Pressure Noninvasively during Mechanical Ventilation: Ready for Prime Time

Jose Dianti, M.D., Ewan C. Goligher, M.D., Ph.D., F.R.C.P.C.

Monitoring and managing spontaneous breathing during mechanical ventilation is a routine clinical challenge for clinicians caring for patients with acute respiratory failure. When the respiratory muscles contract in synchrony with the ventilator, the pressure applied to the lung by the respiratory muscles adds to the pressure applied by the ventilator, increasing the total pressure applied across the lung. Respiratory effort is often excessive in patients with acute respiratory failure,[1] and the resulting high lung-distending pressures may further worsen lung injury (a phenomenon referred to as patient self-inflicted lung injury).[2] Vigorous respiratory efforts can also cause diaphragm myotrauma. On the other hand, when respiratory effort is insufficient, patients are at high risk for diaphragm disuse atrophy. Given increasing evidence of the physiologic and clinical relevance of

"[Inspiratory occlusion pressure and airway occlusion pressure are] simple and noninvasive methods to monitor the risk of lung and diaphragm injury in patients with acute respiratory failure."

In this edition of Anesthesiology, de Vries *et al.*[4] evaluated the performance of two noninvasive techniques for monitoring respiratory effort and lung-distending pressure: the inspiratory occlusion pressure (Pocc), and the airway occlusion pressure in the first 100 ms ($P_{0.1}$). Using data from 38 patients enrolled in a randomized trial testing a strategy to facilitate safe spontaneous breathing during mechanical ventilation, they demonstrate the utility of these measurements to monitor diaphragmatic effort and lung-distending pressure during mechanical ventilation. Specifically, they show that Pocc and $P_{0.1}$ can accurately detect (1) very low diaphragmatic effort, (2) very high diaphragmatic effort, and (3) potentially injurious levels of transpulmonary driving pressure or transpulmonary mechan-


EDITORIAL

Monitoring Respiratory Effort and Lung-distending Pressure Noninvasively during Mechanical Ventilation: Ready for Prime Time

Jose Dianti, M.D., Ewan C. Goligher, M.D., Ph.D., F.R.C.P.C.

"…[de Vries et al.] show that Pocc and P0.1 can accurately detect (1) very low diaphragmatic effort, (2) very high diaphragmatic effort, and (3) potentially injurious levels of transpulmonary driving pressure or transpulmonary mechanical power."


EDITORIAL

Monitoring Respiratory Effort and Lung-distending Pressure Noninvasively during Mechanical Ventilation: Ready for Prime Time

Jose Dianti, M.D., Ewan C. Goligher, M.D., Ph.D., F.R.C.P.C.

"The study by de Vries et al. substantially strengthens the growing body of data on the validity of both P0.1 and Pocc as simple and noninvasive methods to monitor the risk of lung and diaphragm injury in patients with acute respira-tory failure. Analogous to routine measurement of plateau pressure and driving pressure during passive ventilation, P0.1 and Pocc provide invaluable information on the safety and appropriateness of mechanical ventilation."

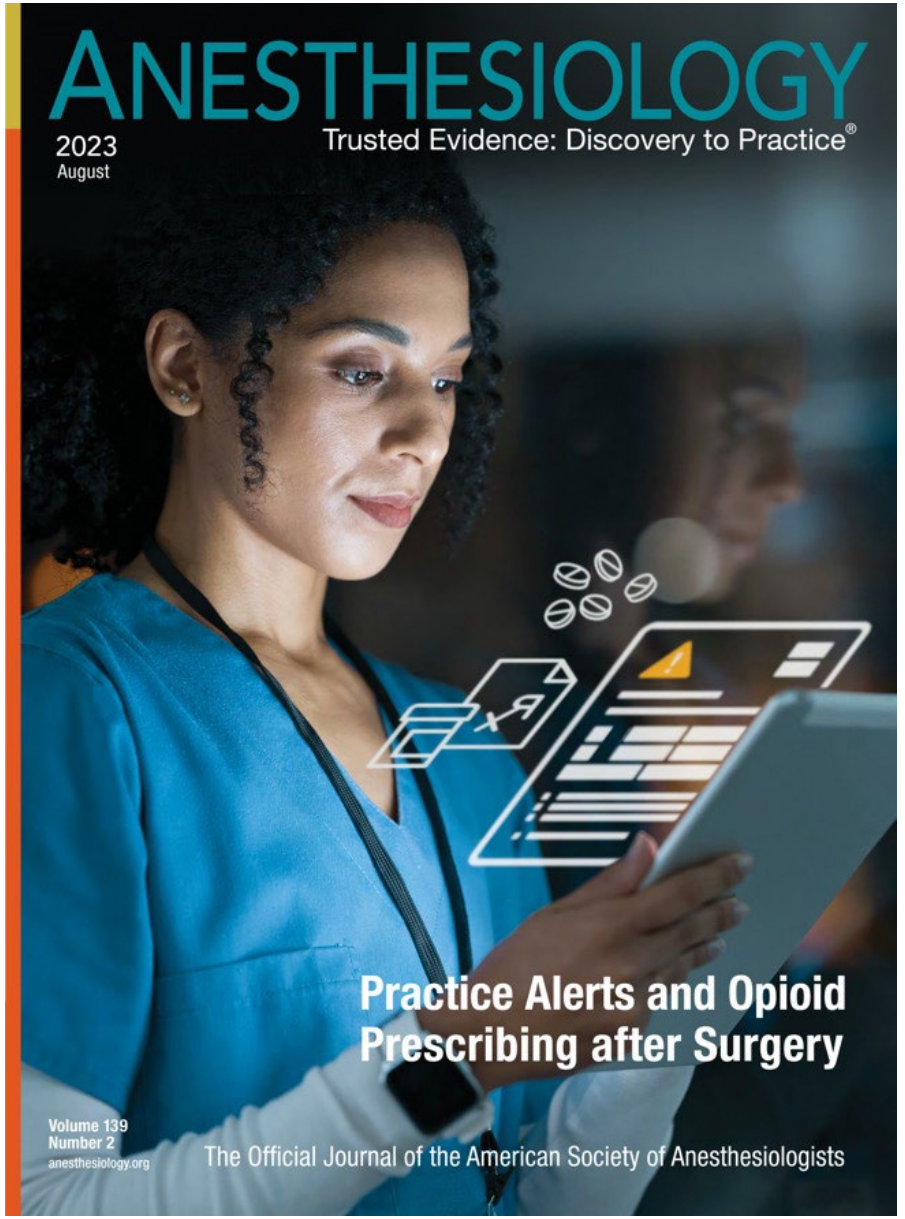
PAIN MEDICINE

ANESTHESIOLOGY

Best Practice Alerts Informed by Inpatient Opioid Intake to Reduce Opioid Prescribing after Surgery (PRIOR): A Cluster Randomized Multiple Crossover Trial

Megan L. Rolfzen, M.D., Abraham Wick, Pharm.D., Edward J. Mascha, Ph.D., Karan Shah, M.S., Martin Krause, M.D., Ana Fernandez-Bustamante, M.D., Ph.D., Jean S. Kutner, M.D., M.S.P.H., P. Michael Ho, M.D., Ph.D., F.A.C.C., Daniel I. Sessler, M.D., Karsten Bartels, M.D., Ph.D., M.B.A.

ANESTHESIOLOGY 2023; 139:186–96



EDITOR'S PERSPECTIVE

What We Already Know about This Topic

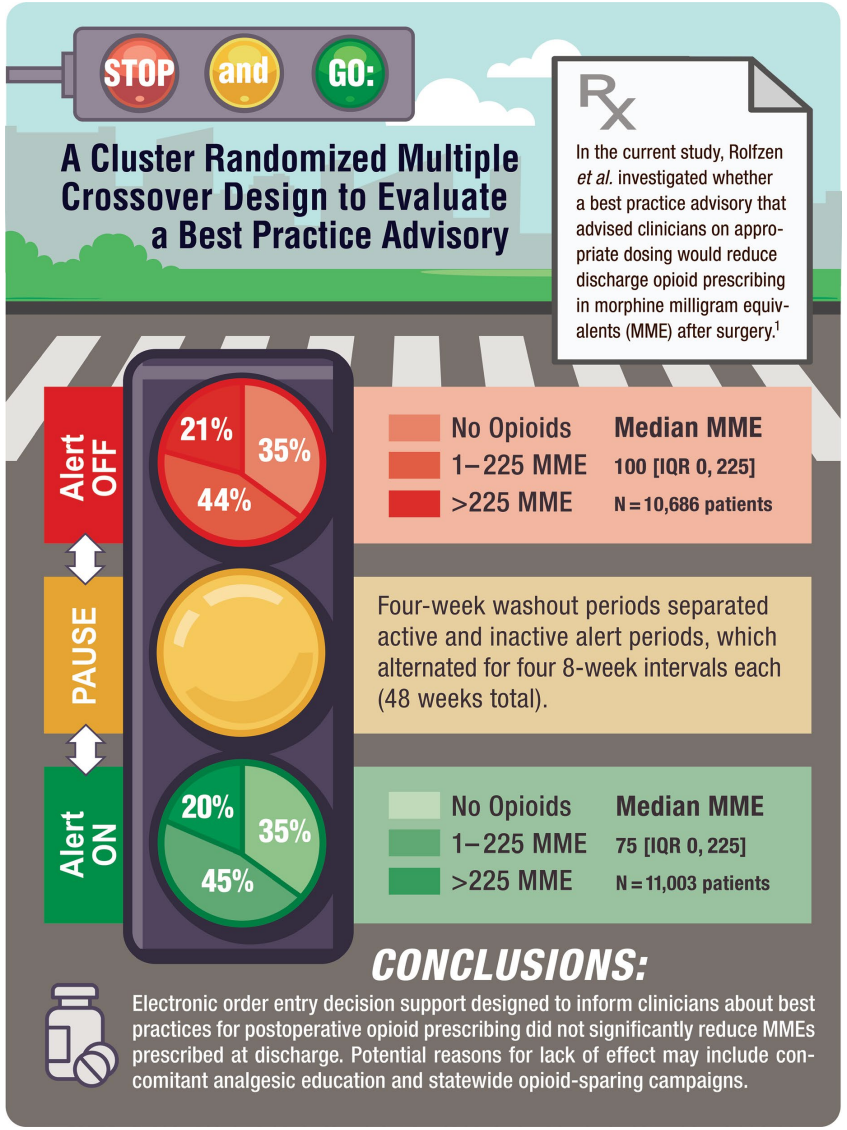
- Opioid overprescription at the time of surgery may lead to leftover opioids available for diversion or misuse
- Decision-support tools embedded in electronic health records have been shown to improve outcomes in other contexts

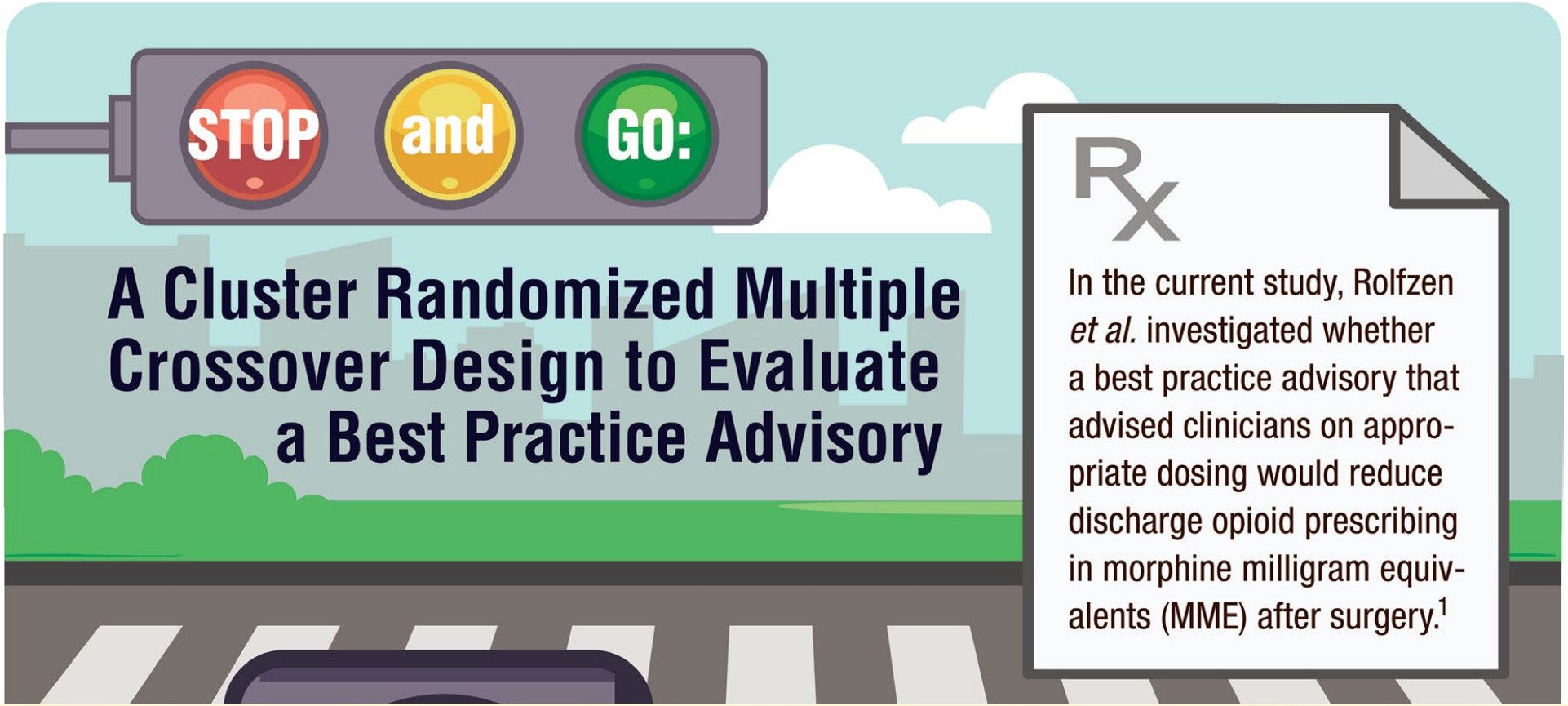
What This Article Tells Us That Is New

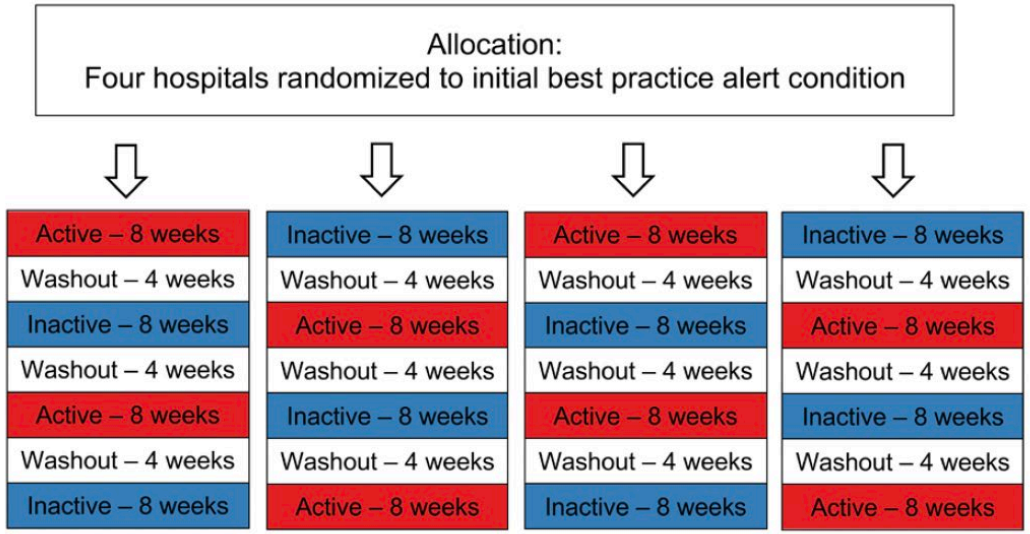
- In this cluster randomized multiple crossover trial, four hospitals were randomized to alternating 8-week periods with an electronic decision-support tool that recommended tailored discharge opioid prescriptions based on previous inpatient opioid intake
- There was no difference in the primary outcome of oral morphine milligram equivalents prescribed at discharge
- In the setting of extensive education and increasing awareness of the risks of overprescription, electronic opioid prescription guidance did not significantly reduce opioid prescribing

INFOGRAPHICS IN ANESTHESIOLOGY

Complex Information for Anesthesiologists Presented Quickly and Clearly




STOP and GO:
A Cluster Randomized Multiple Crossover Design to Evaluate a Best Practice Advisory
Rx
In the current study, Rolfzen *et al.* investigated whether a best practice advisory that advised clinicians on appropriate dosing would reduce discharge opioid prescribing in morphine milligram equivalents (MME) after surgery.[1]


Allocation:
Four hospitals randomized to initial best practice alert condition
Active – 8 weeks
Washout – 4 weeks
Inactive – 8 weeks
Washout – 4 weeks
Active – 8 weeks
Washout – 4 weeks
Inactive – 8 weeks
Inactive – 8 weeks
Washout – 4 weeks
Active – 8 weeks
Washout – 4 weeks
Inactive – 8 weeks
Washout – 4 weeks
Active – 8 weeks
Active – 8 weeks
Washout – 4 weeks
Inactive – 8 weeks
Washout – 4 weeks
Active – 8 weeks
Washout – 4 weeks
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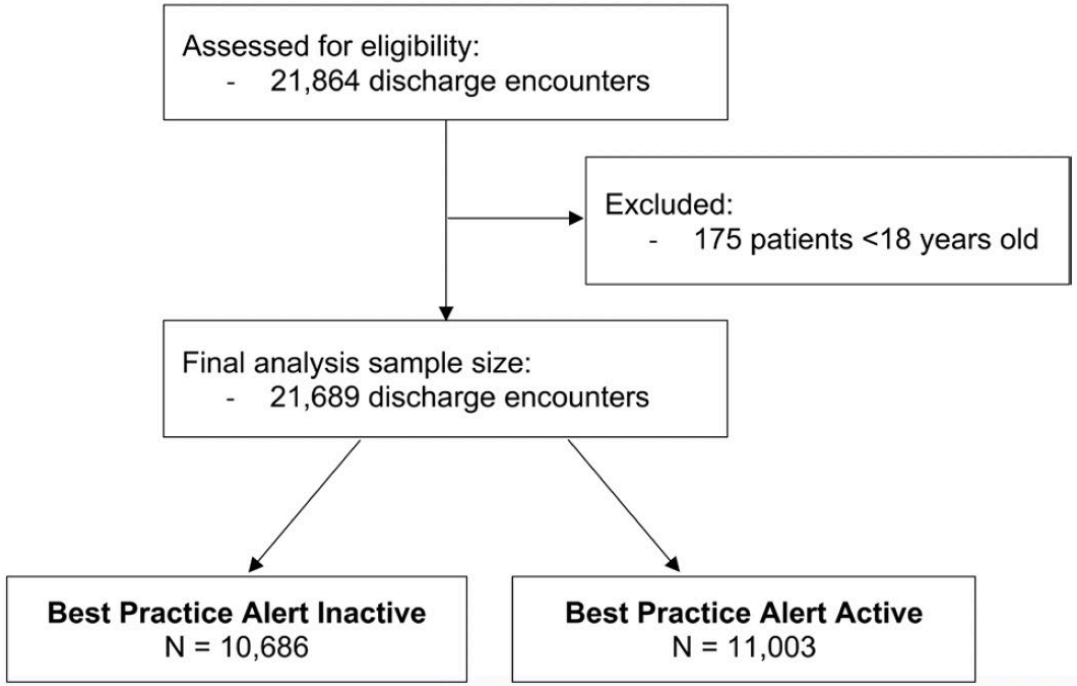
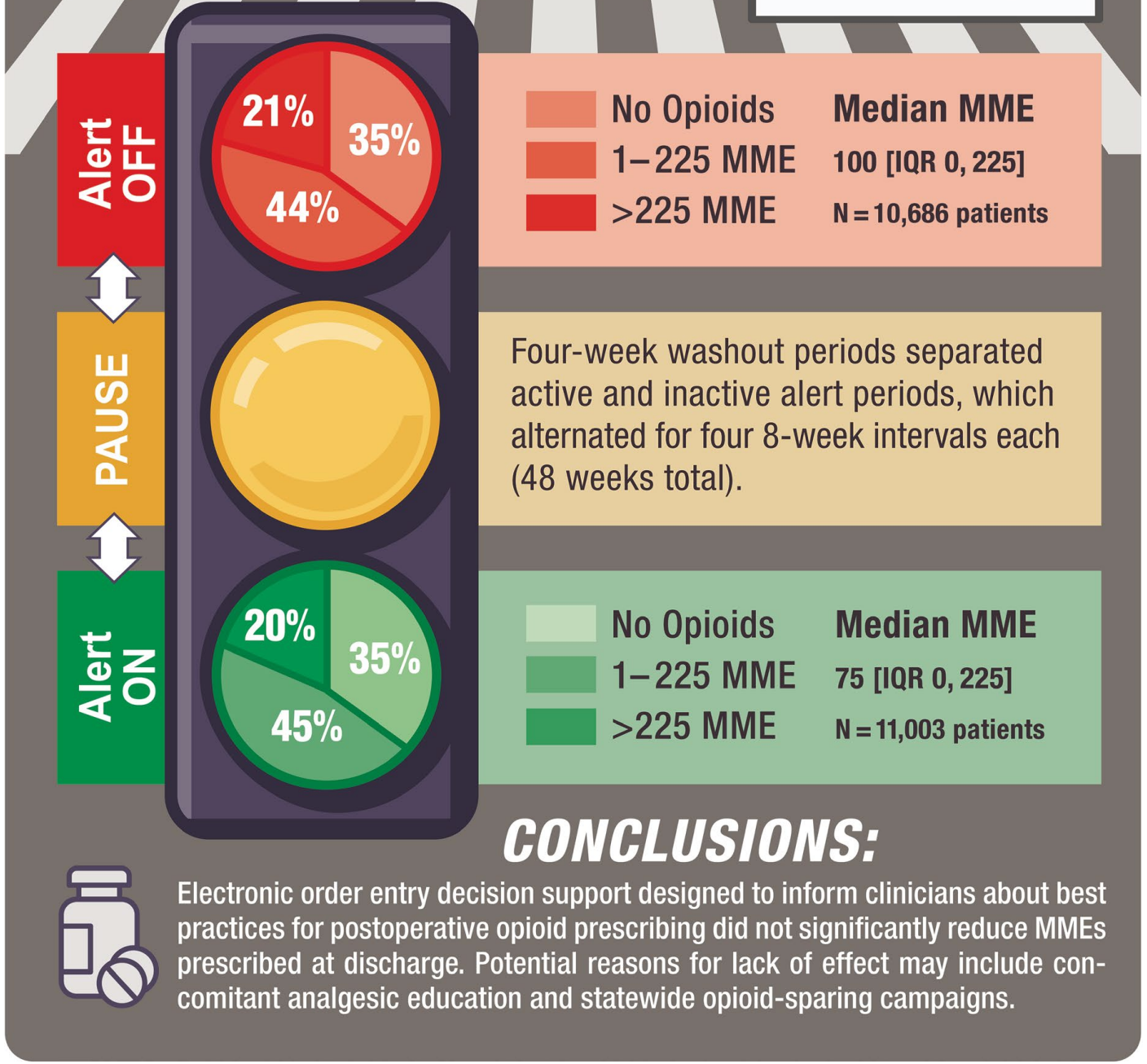
Inactive – 8 weeks
Washout – 4 weeks
Active – 8 weeks


Assessed for eligibility:
- 21,864 discharge encounters
Excluded:
- 175 patients <18 years old
Final analysis sample size:
- 21,689 discharge encounters
Best Practice Alert Inactive
N = 10,686
Best Practice Alert Active
N = 11,003



CONCLUSIONS:

Electronic order entry decision support designed to inform clinicians about best practices for postoperative opioid prescribing did not significantly reduce MMEs prescribed at discharge. Potential reasons for lack of effect may include concomitant analgesic education and statewide opioid-sparing campaigns.

Best Practice Alerts: A Poke in the Eye or an Efficient Method for Safer Prescribing?

Chad M. Brummett, M.D., Zachary Wagner, Ph.D., Jennifer F. Waljee, M.D., M.P.H., M.S.

Opioid-related morbidity and overdose continues to accelerate in the United States, with more than 80,000 opioid-related deaths reported in 2021. Whereas the increase in overdose in recent years is largely due to heroin and illicit fentanyl, most who develop opioid use disorder begin with an exposure to opioid pills.[1] One of the most common reasons for opioid prescribing is to manage acute postoperative pain, and postoperative opioid prescribing in the United States has been marked by excess and risky patterns given a lack of evidence-based prescribing guidelines. Furthermore, opioid disposal strategies remain widely underutilized due to a lack of convenience and fears that opioid medications may not be available for future need. Excessive prescribing is correlated with persistent opioid use,[2] which has been linked to increased hospital utilization,

"Despite the strong rationale for prescribing guidelines, implementation of evidence often takes many years, and there is an urgent need for novel ways to align postoperative prescribing with patient need and eliminate excessive prescribing."

care has been associated with decreases in postsurgical prescribing and persistent use,[3] these effects are concentrated among areas where uptake may be higher. Moreover, a recent study examining prescribing practices among surgeons in the United States in 2019 demonstrates that high rates of risky prescribing practices persist. Despite the strong rationale for prescribing guidelines, implementation of evidence often takes many years, and there is an urgent need for novel ways to align postoperative prescribing with patient need and eliminate excessive prescribing. In this issue of Anesthesiology, Dr. Rolfzen *et al.* studied the use of a best practice alert in the electronic health record in a clinical trial entitled, "Best


EDITORIAL

Best Practice Alerts: A Poke in the Eye or an Efficient Method for Safer Prescribing?

Chad M. Brummett, M.D., Zachary Wagner, Ph.D., Jennifer F. Waljee, M.D., M.P.H., M.S.

"While the best practice alert tested in the trial by Rolfzen and colleagues did not change post-discharge opioid prescribing overall, the authors identified opportunities for future applications among settings with a higher rate of excessive prescribing. Going for-ward, it is critical to continue to study best practice alerts and other interventions in future, including default recommendations and provider feedback."

Best Practice Alerts Informed by Inpatient Opioid Intake to Reduce Opioid Prescribing after Surgery (PRIOR)

A cluster randomized multiple crossover trial across 4 hospitals in Colorado

Electronic decision-support tool provided discharge opioid prescription recommendation based on inpatient opioid intake

- 21,689 surgical inpatient discharges
- Cluster randomization of **Alert *vs.* No Alert** across alternating 8-week periods

		
Oral morphine equivalents prescribed, median [IQR]	75 [0, 225]	100 [0, 225]

$P = 0.6$

Use of an electronic decision-support tool was not associated with a significant reduction in discharge opioid prescribing after surgery

Rolfzen ML, *et al.* ANESTHESIOLOGY, 2023.

ANESTHESIOLOGY

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Anesthesiology in 2023: Articles You Need to Know

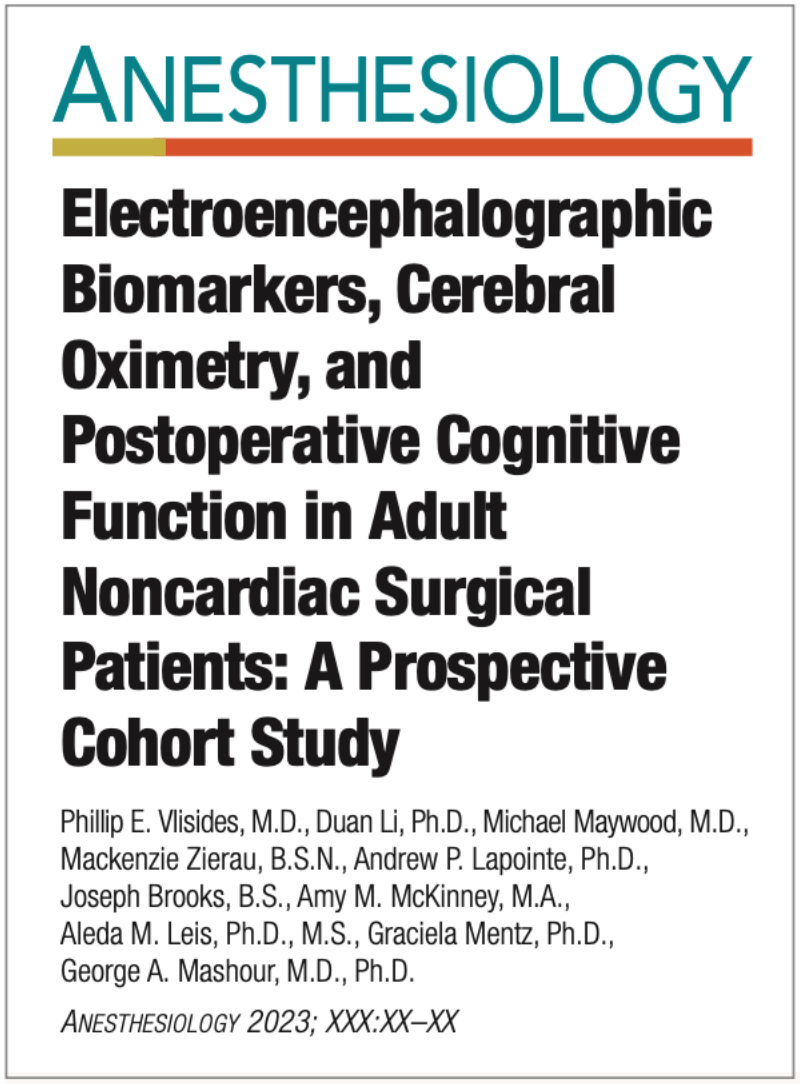
Kristin L. Schreiber, MD/Ph.D.

Editor

PERIOPERATIVE MEDICINE

Anesthesia-induced Brain Oscillations and Vulnerability to Postoperative Neurocognitive Disorders

Rodrigo Gutiérrez, M.D., Ph.D., Patrick L. Purdon, Ph.D.

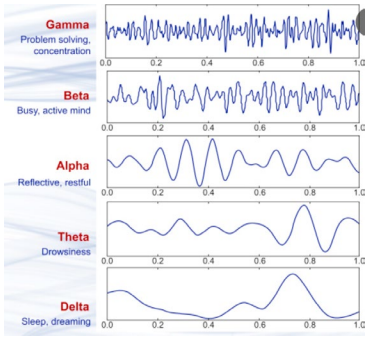


- Can preop (or intraop) EEG and oximetry predict postoperative cognitive dysfunction and delirium?

Post-Operative Cognitive Dysfunction (POCD)

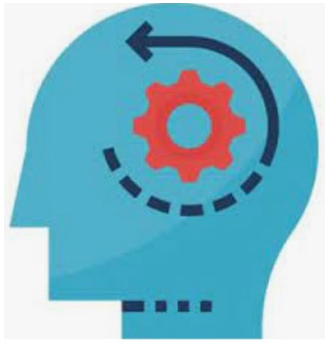
- Cortical information processing underlies POCD
- measurable as disruptions in EEG and cerebral oxygenation
- frontal-parietal alpha connectivity
- intraoperative EEG suppression
- decreased cerebral oximetry
- Are these also associated with POCD?

Cortical information processing



EEG

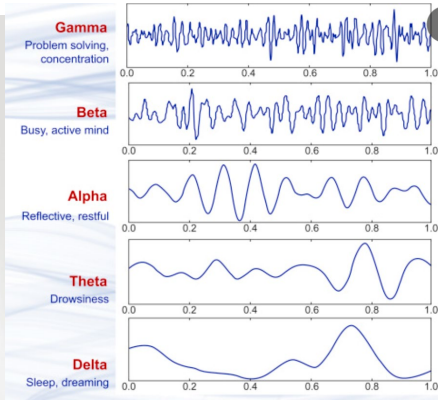
Cerebral oximetry



POCD

Methods

- Single-center observational study
- 64 adult patients undergoing surgery under general anesthesia
- Exposure/Predictor Variables (EEG and oximetry)
    - preoperative relative posterior alpha power;
    - preoperative minus PACU relative posterior alpha power
    - preoperative frontal-parietal connectivity
    - preoperative minus PACU frontal-parietal connectivity
    - intraoperative theta connectivity state occurrence rate
    - average preoperative cerebral oximetry values

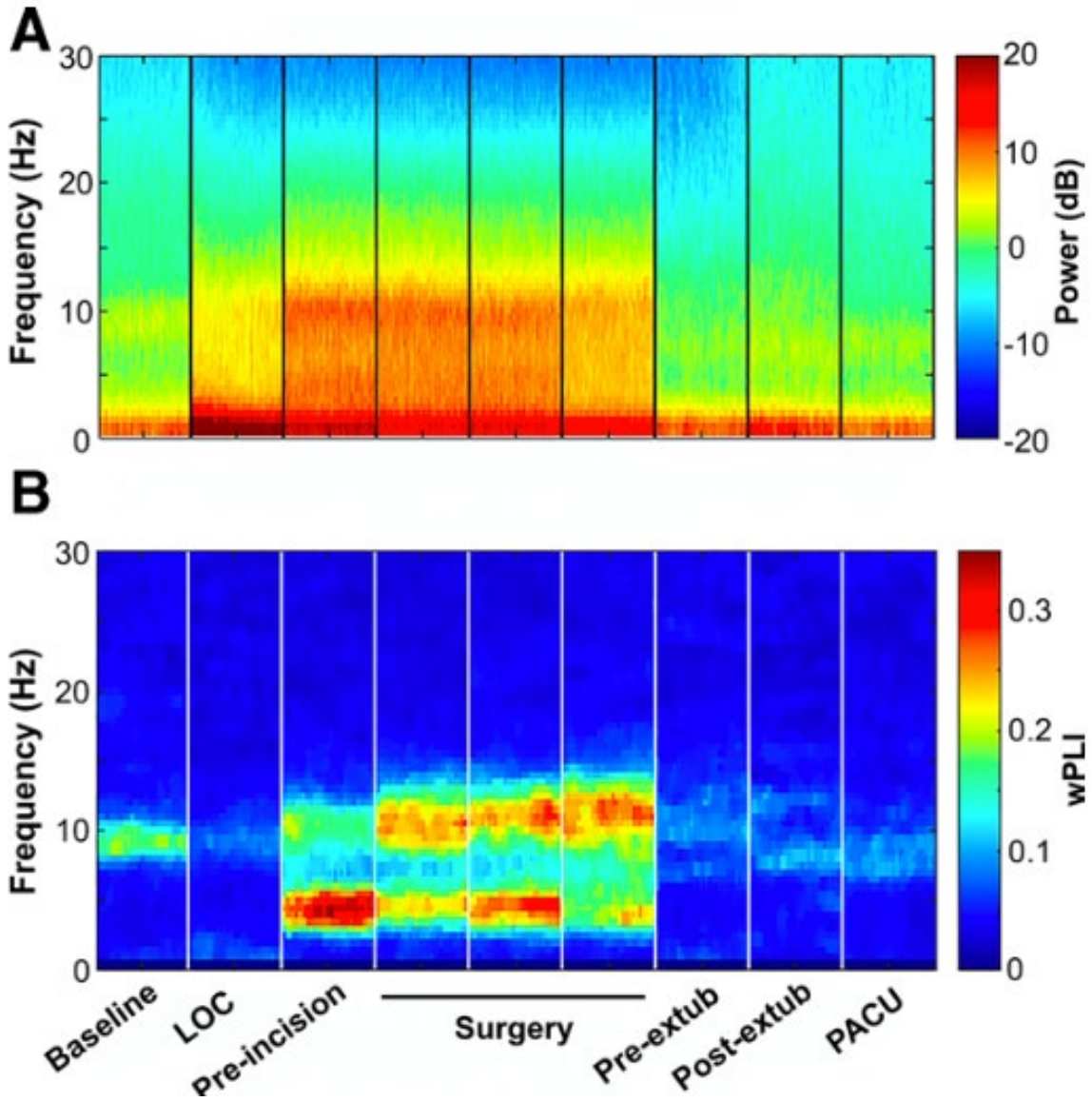


- Primary outcome: POCD (lowest NIH Cognition Toolbox score during POD1-2)
    - Flanker Inhibitory Control and Attention Test (Executive Function and Attention)
    - List Sorting Working Memory Test
    - Pattern Comparison Processing Speed Test
    - fully corrected T-scores (age, sex, race, ethnicity, and level of education) from 3 tests

- Secondary outcome: Delirium
    - Confusion Assessment Method (3-min diagnostic version)
- Partial correlations and Generalized estimating equations to test association between exposure and outcome Variables

Spectral and connectivity data (n=52)

Spectrogram: Representation of different frequencies over time



- During anesthesia, spectrograms reveal a predominance of frontal alpha, theta, and delta oscillatory power

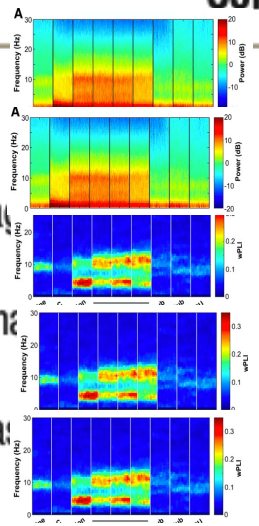
weighted phased lag index:

- surrogate marker of functional connectivity
- who is talking to whom
- at what frequency

- Connectivity data demonstrate
- →coherent frontal-parietal alpha connectivity at baseline
- →alpha- and theta-dominant frontal-parietal connectivity intraoperatively
- →reduced frontal-parietal alpha connectivity during PACU recovery

Association of Features with Postop Cognitive Function

Preoperative Neurophysiologic Measure	Partial Spearman Correlation (ρ)	*P* Value	Adjusted Estimate (β)	95% CI	*P* Value
Baseline relative parietal alpha (%)	–0.03	0.854	–0.04	–0.15 to 0.08	0.552
Baseline-PACU parietal alpha (%)	–0.19	0.309	–0.12	–0.26 to 0.02	0.102
Baseline frontal-parietal alpha weighted phase lag index (n)	–0.10	0.570	–3.43	–20.02 to 13.17	0.686
Baseline-PACU frontal-parietal alpha weighted phase lag index (n)	–0.19	0.305	–3.69	–16.65 to 9.27	0.577
Intraoperative theta frontal-parietal weighted phase lag index occurrence rate (%)	–0.25	0.171	–1.40	–11.05 to 8.25	0.776
Average baseline cerebral oximetry (%)	0.21	0.246	0.16	–0.04 to 0.36	0.107

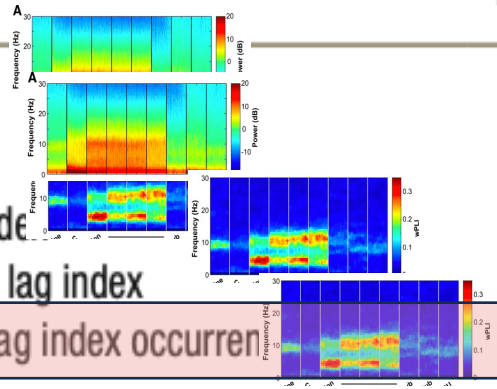


Partial correlation coefficients and sequential generalized estimating equation model estimates presented. Partial correlation analysis controls for the fully corrected baseline mean

- EEG parameters carefully measured in pre- and intraop period
- tested for association with postoperative cognitive function
- None were significantly associated

Association of Features with Postop Delirium

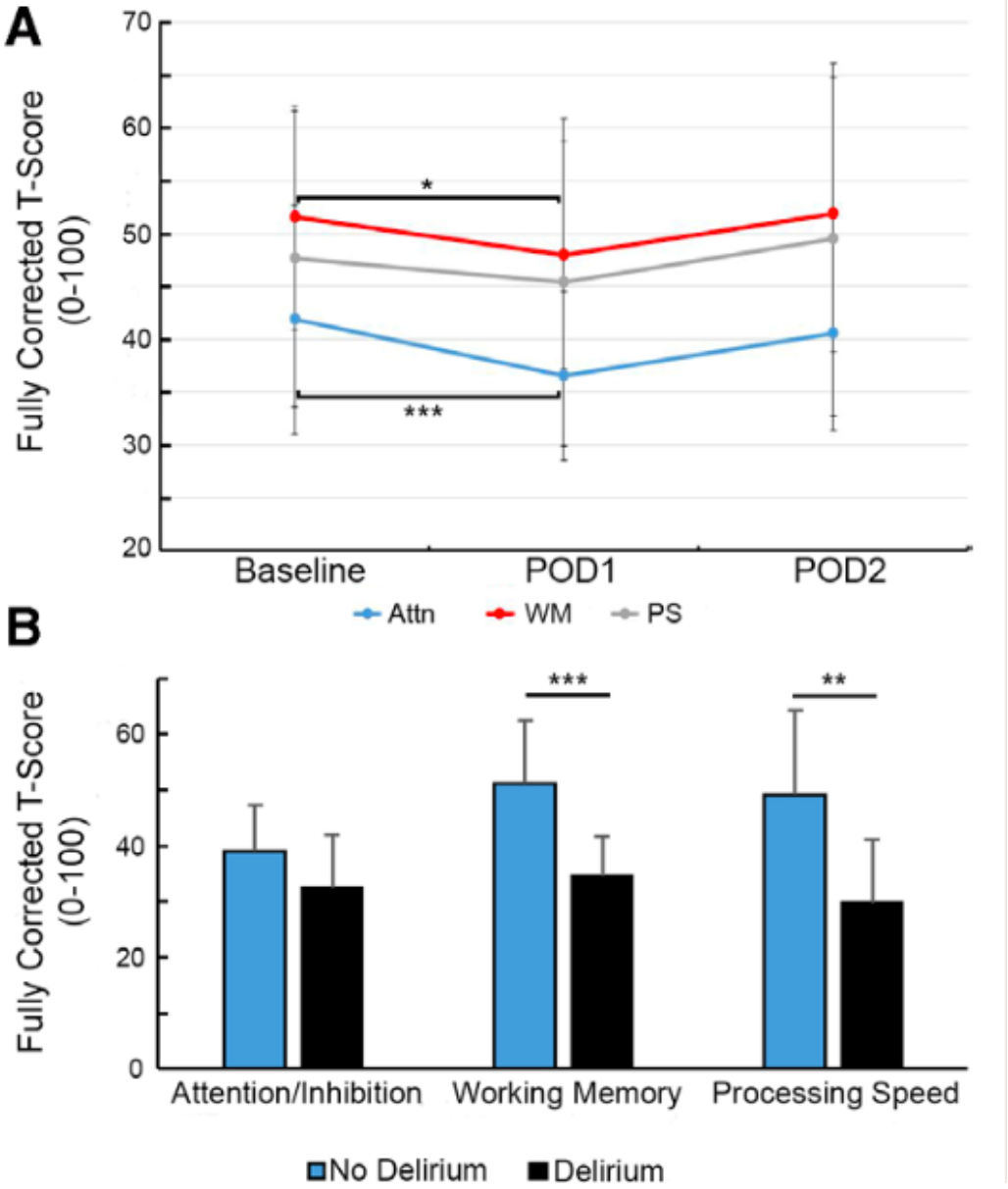
Preoperative Neurophysiologic Measure	Participants	Repeated Measures	Degrees of Freedom	F Statistics	*P* Value
Baseline relative parietal alpha (%)	47	288	(1,6,281)	0.18	0.674
Baseline-PACU parietal alpha (%)	38	236	(1,6,229)	0.01	0.913
Baseline frontal-parietal alpha weighted phase lag inde	47	288	(1,6,281)	0.27	0.606
Baseline-PACU frontal-parietal alpha weighted phase lag index	40	246	(1,6,239)	0.02	0.887
Intraoperative theta frontal-parietal weighted phase lag index occurren	49	298	(1,6,291)	4.53	0.034
Average baseline cerebral oximetry (%)	56	334	(1,6,327)	0.85	0.358



- Most were not were significantly associated
- only intraoperative theta fronto-parietal connectivity was associated with postoperative delirium

Relationship between POCD and Delirium

- Delirium associated with decreased scores on some formal tests
- Working memory
- Processing speed
- Not attention



Summary

intraoperative EEG pattern(s) ⟷ POCD Delirium

- Employed robust methodology to test whether preoperative brain signals (EEG) could predict POCD

<u>Primary Outcomes:</u>

- No <u>preop</u> EEG features can easily predict POCD or delirium
  - Preoperative and PACU relative alpha power not associated with POCD
  - Alpha and theta frontoparietal functional connectivity not associated with POCD
  - Cerebral oximetry was not related to POCD

<u>Secondary Outcomes:</u>

- Only intraoperative frontoparietal theta connectivity was associated with postoperative delirium

- Potential for changes in intraoperative EEG features to reveal brain vulnerability

EDITORIAL

Consideration of Methadone as an Analgesic Option for Short-stay Surgery

Paul S. Myles, M.B., B.S., M.P.H., M.D., D.Sc., F.C.A.I., F.A.N.Z.C.A., F.A.H.M.S., Chad M. Brummett, M.D.

- What is the right dose of methadone to use in the periop period?
- Does it really work?
- Doesn't it have side effects that I have to worry about after my patient goes home?

ANESTHESIOLOGY

Intraoperative Methadone in Next-day Discharge Outpatient Surgery: A Randomized, Double-blinded, Dose-finding Pilot Study

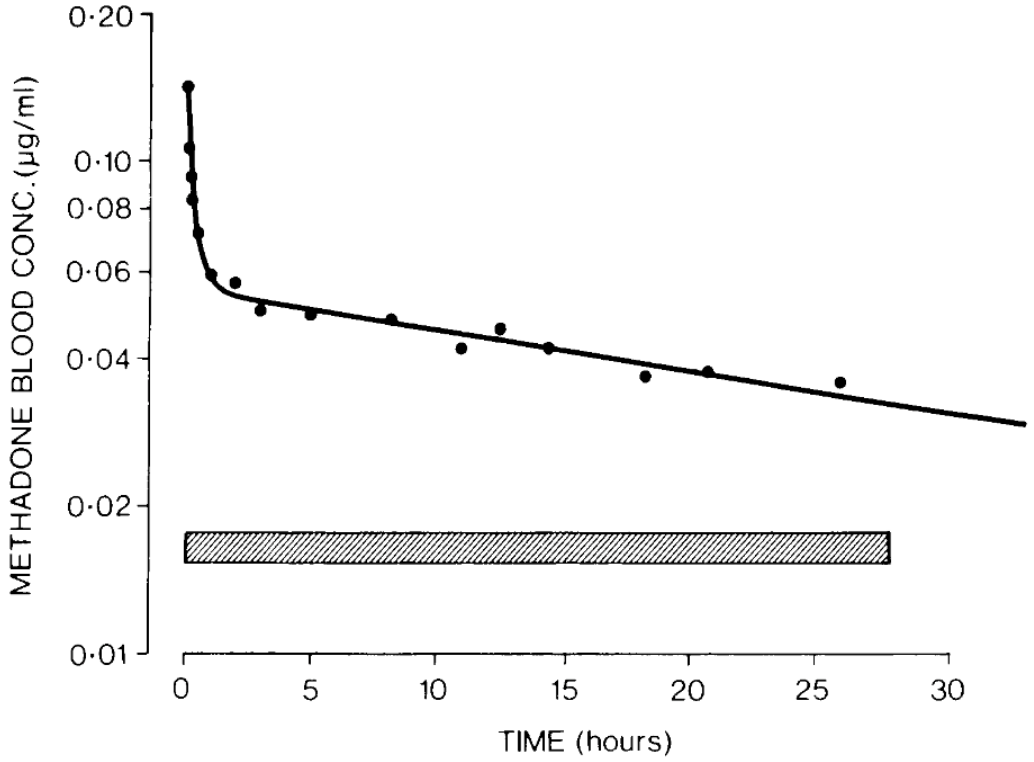
Evan D. Kharasch, M.D., Ph.D., L. Michael Brunt, M.D., Jane Blood, R.N., Helga Komen, M.D.

ANESTHESIOLOGY 2023; 139:405–19

- More than 50 million outpatient surgical procedures in the United States (70%)
- After going home, patients self-manage their pain
- Opioids are effective at reducing moderate to severe postoperative pain
- Mixed success of developing and marketing long-acting, slow-release opioids
- Advantages of long-acting opioids
  - less rebound
  - less reward
  - better coverage
  - less post-discharge opioid prescribing

Methadone

- Recently rediscovered, with increased perioperative use
- Synthetic long-acting opioid agonist (mu)
- weak N-methyl-d-aspartate receptor antagonist
- Peak effect site concentration achieved 8 min after IV admin
- long and variable elimination half-life of 24 to 36 h
- elimination clearance determines duration of analgesia, therefore advantageous to use highest possible effective and safe bolus dose (maximize duration)
- Methadone administration may spare the use of other opioids
- 30 to 40% less postoperative pain and opioid use, and greater patient satisfaction
- Is it safe for people going home the same day?
- What is the dose that should be used?



Gourlay GK, Wilson PR, Glynn CJ: Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 1982; 57:458–67

- Feasibility study→ to inform design of future larger RCT
- Determine the suitability of single-dose intraoperative methadone for outpatient surgery
- identify an optimal single dose (exploratory)
  - analgesic efficacy
  - well-tolerated
  - explore impact on administration of postoperative other opioid use

Methods

- Phase 2b trial→ dose finding
- undergoing elective outpatient surgery under general anesthesia with next-day discharge
- Exclusion criteria: history of liver or kidney disease, potentially opioid tolerance
- Increasing doses of methadone: 0.1, 0.2, 0.25 and 0.3mg/kg, ideal body weight (20 mg cap)
- 2:1 methadone:treatment as usual

Blinding:

- Investigators, patients, and research staff blinded
- Anesthesia providers and postanesthesia care unit (PACU) nurses unblinded

Methadone administration:

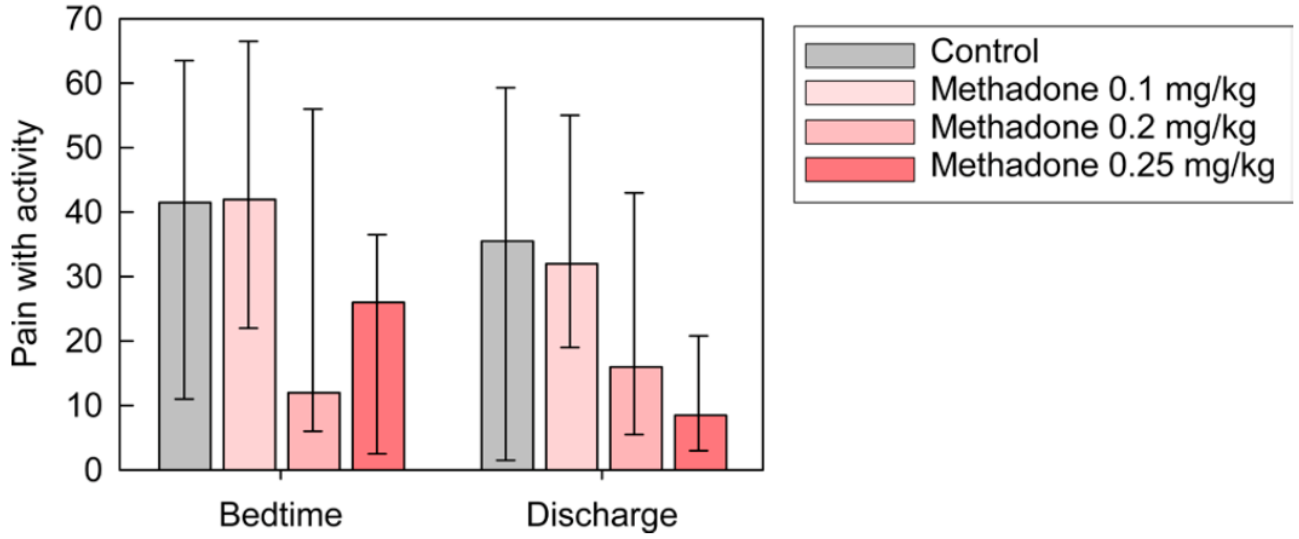
- single dose, in the operating room during or <10 min before induction
- no additional short-duration opioid during the procedure in subjects receiving methadone
- additional short-duration opioid for pain as needed during or after wound closure and emergence
- vs treatment as usual (choice of fentanyl, sufentanil, hydromorphone, or morphine, at practitioners' discretion)

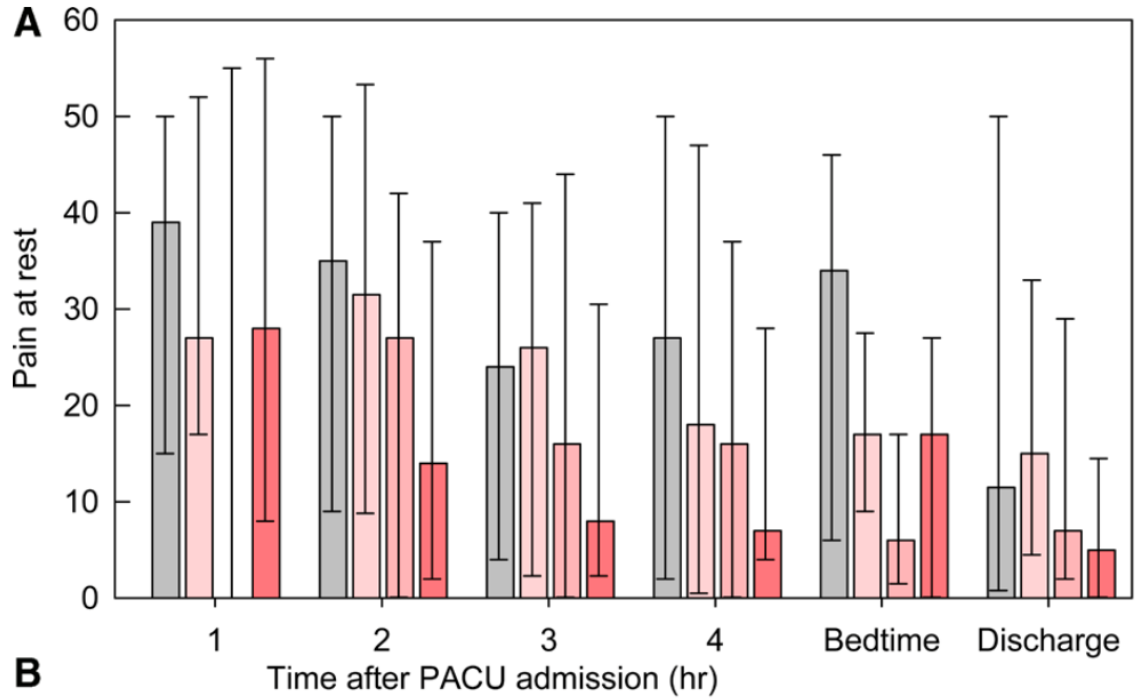
	Control (Usual Care, Short-duration Opioid)	Methadone Dose (mg/kg Ideal Body Weight)			
		0.1 mg/kg	0.2 mg/kg	0.25 mg/kg	0.3 mg/kg
No.	40	19	23	21	21
Age (yr)	47 ± 10	52 ± 8	51 ± 9	52 ± 10	49 ± 9
Actual weight (kg)	88 ± 27	84 ± 19	91 ± 21	83 ± 22	90 ± 27
Ideal body weight (kg)	56 ± 6	58 ± 10	55 ± 7	57 ± 8	58 ± 6
Sex (male: female)	0:40	3:16	1:22	0:21	0:21
Race (white/ black/other)	31/9/0	17/2/0	18/5/0	16/5/0	19/2/0
ASA risk status (1/2/3)	3/34/3	0/16/3	0/18/5	2/19/0	1/15/5
Surgical procedure					
Laparoscopic hysterectomy*	35	11	20	21	17
Laparoscopic hiatal hernia repair	5	8	2	0	3
Vaginal hysterectomy	0	0	1	0	1
Anesthesia duration (min)	164 ± 47	156 ± 50	175 ± 56	178 ± 56	188 ± 57
Returned 30-d diary	28	11	20	19	11
	70%	58%	87%	90%	52%

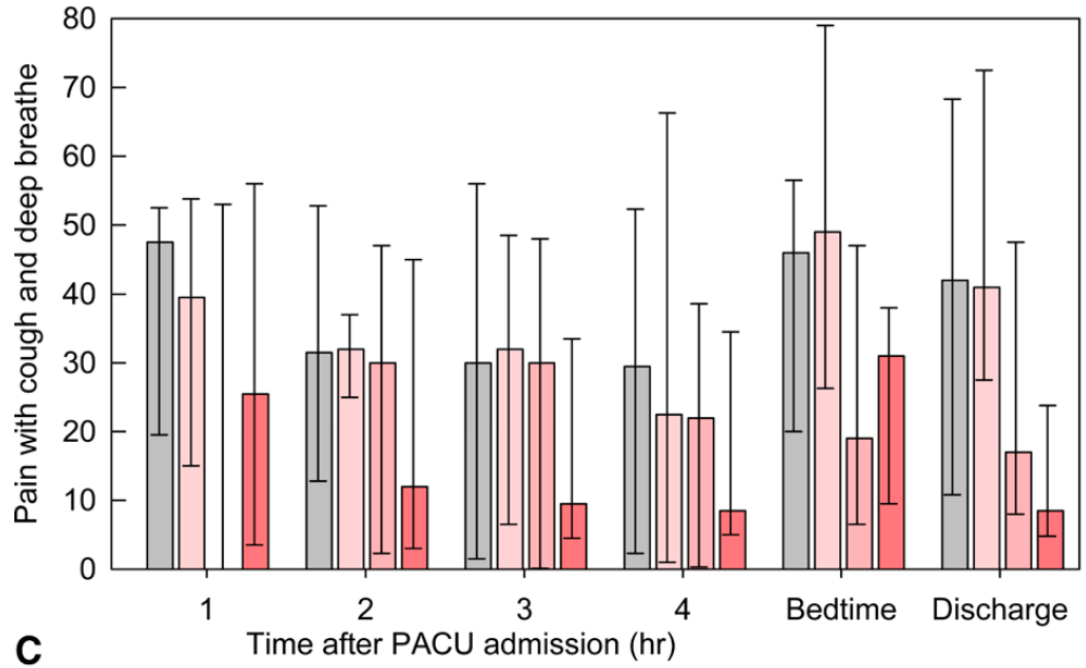
- 18 to 65 yr old (N=129)
- Enrolled 12/2014-11/2018
- predominantly women undergoing laparoscopic or vaginal hysterectomy, lap hiatal hernia repair
- Postdischarge data capture with variable success

Pain while in hospital

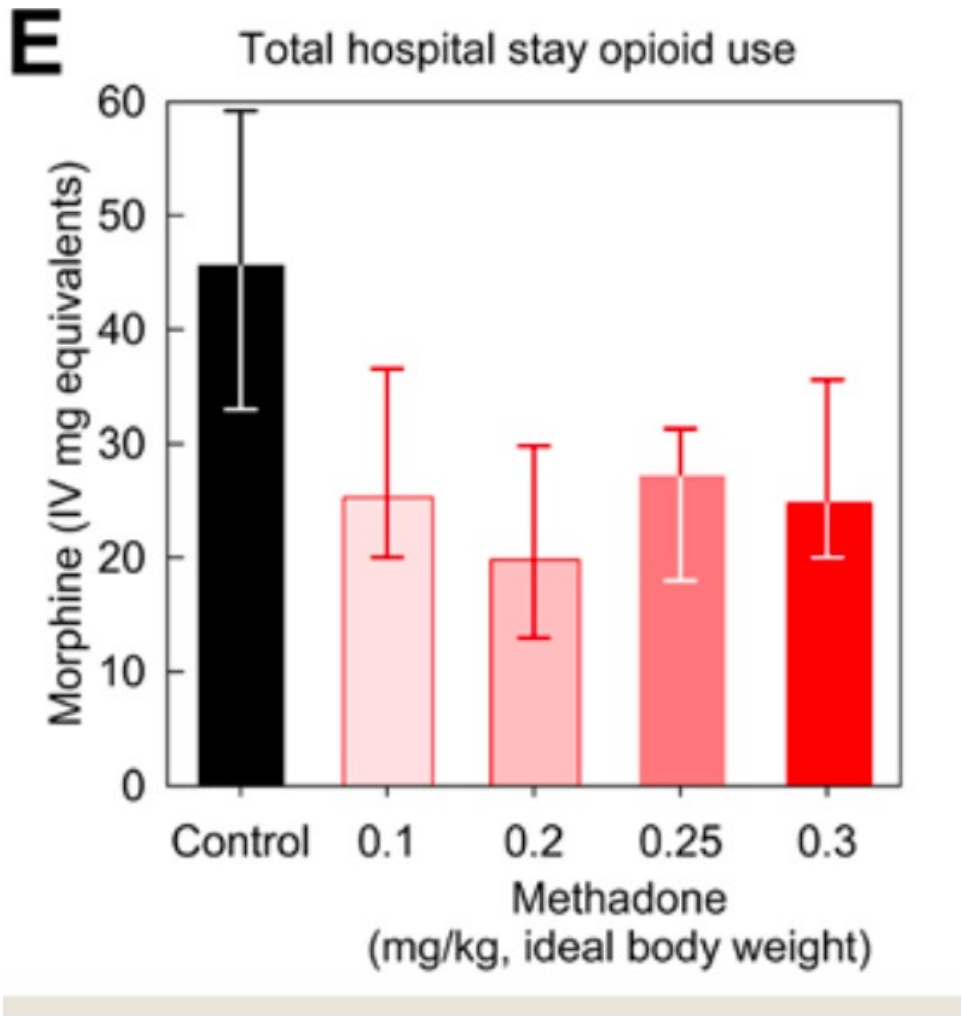
- Signal of a dose-related analgesic effect

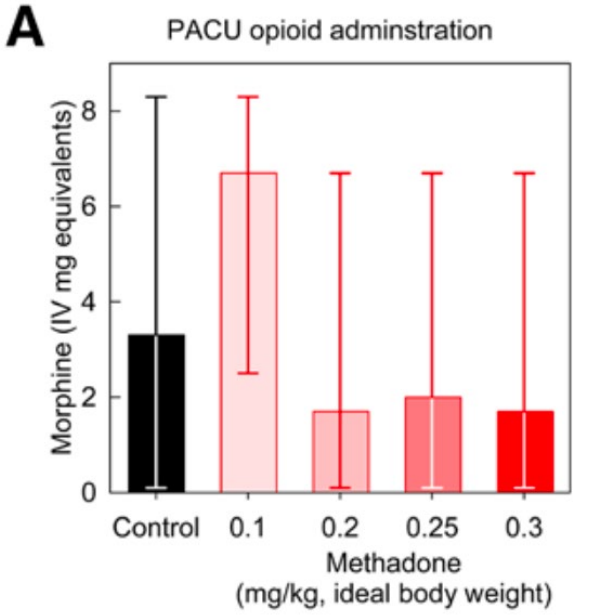


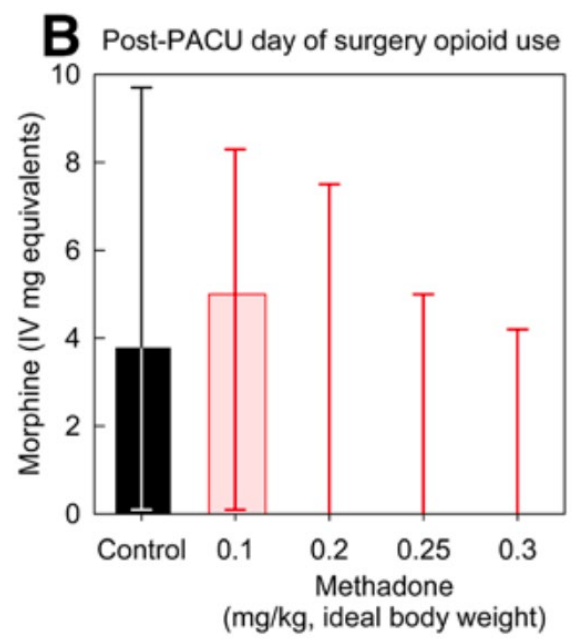




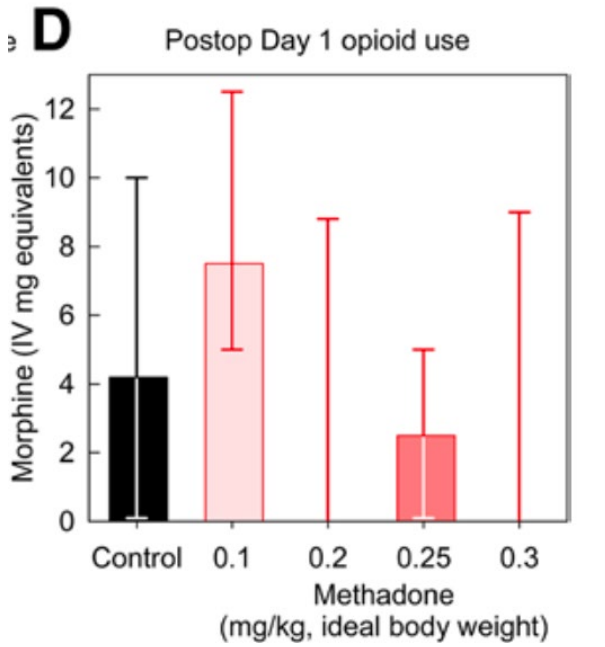
In hospital opioid use





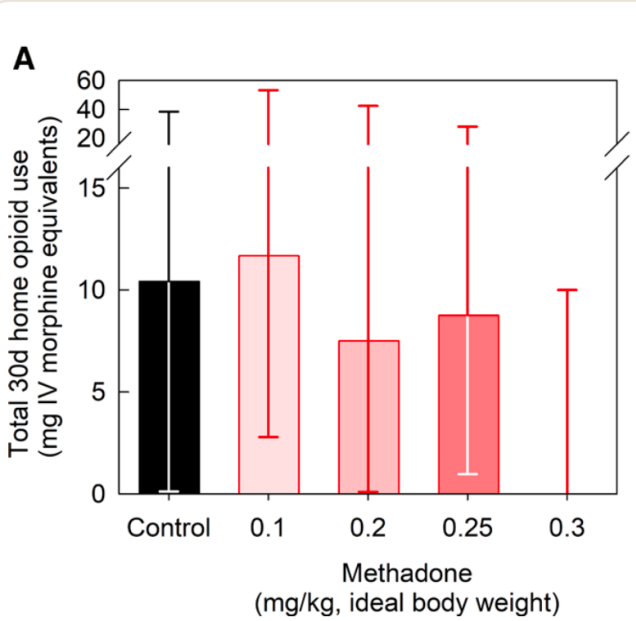


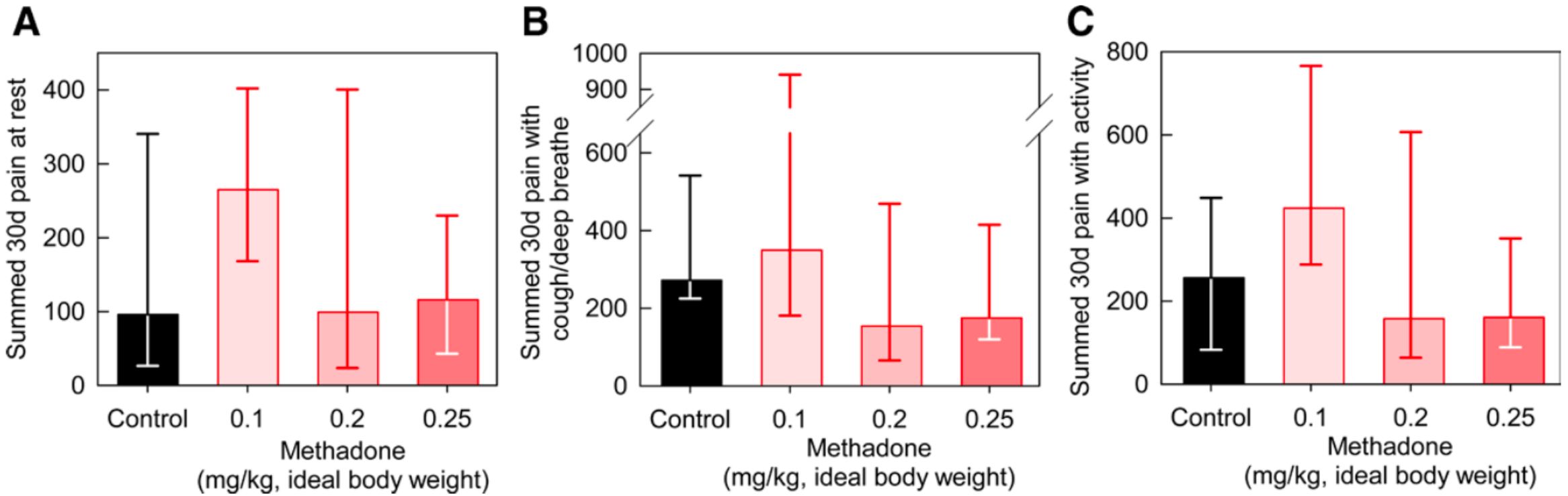
- Signal of less inpatient opioid use (short-acting)



Pain and Opioid use after discharge

- Signal of less pain and opioid use





Feasibility aims:

- 55% of eligible patients willing to consent
- 93% anesthesiology providers compliant with the protocol
- 96% completion of in-hospital patient follow-up measures
- 72% average completion of patient-reported outcome surveys

Exploratory aims:

- intraoperative dose that best combined opioid sparing, analgesia, and minimization of adverse events: 0.25mg/kg ideal body weight (median:14 mg, 25th to 75th percentiles:13 to 16 mg)

Considerations:

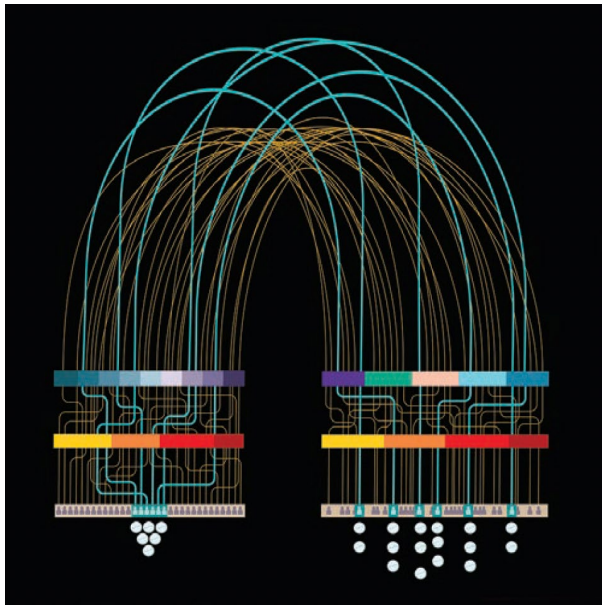
- Multiple testing (type I error warning)
- Small n (type II error warning)
- Adverse effects such as respiratory depression and delayed discharge are rare, and cannot be tested for in this small of a study

EDITORIAL

Uncoupling Pain and Opioid Use after Surgery

Karim Shiraz Ladha, M.D., M.Sc., Kristin L. Schreiber, M.D., Ph.D.

- What factors predict prolonged opioid use after surgery?
- How does it relate to pain?



ANESTHESIOLOGY

Prolonged Opioid Use and Pain Outcome and Associated Factors after Surgery under General Anesthesia: A Prospective Cohort Association Multicenter Study

Kai Kuck, Ph.D., Bhiken I. Naik, M.B.B.Ch., M.S.C.R., Karen B. Domino, M.D., M.P.H., Karen L. Posner, Ph.D., Leif Saager, M.D., Ami R. Stuart, Ph.D., Ken B. Johnson, M.D., Salome B. Alpert, Ph.D., Marcel E. Durieux, M.D., Ph.D., Anik K. Sinha, M.S., Chad M. Brummett, M.D., Michael F. Aziz, M.D., Kenneth C. Cummings III, M.D., John G. Gaudet, M.D., Andrea Kurz, M.D., Mienke Rijsdijk, M.D., Ph.D., Jonathan P. Wanderer, M.D., Nathan L. Pace, M.D., M.Stat., and the Multicenter Perioperative Outcomes Group Enhanced Observation Study Investigator Group for the Multicenter Perioperative Outcomes Group Enhanced Observation Study Collaborator Group*

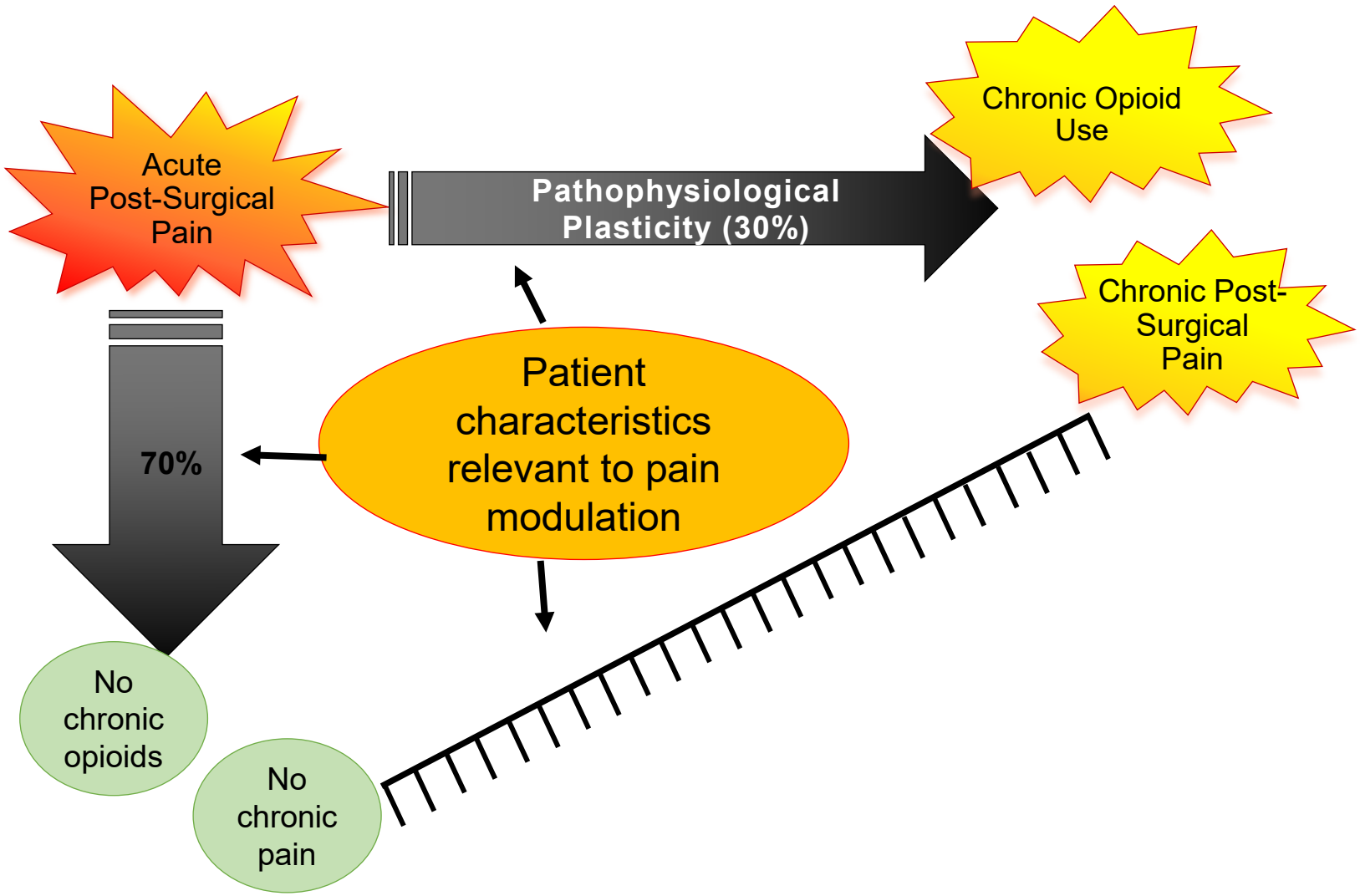
ANESTHESIOLOGY 2023; 138:462–76

Scan for CME exam

Predicting and Understanding Variation in postsurgical pain and opioid use

1. Chronic pain and opioid use relevant only for a minority of patients
2. Pain and opioid use needs to be sensitively and accurately measured in studies

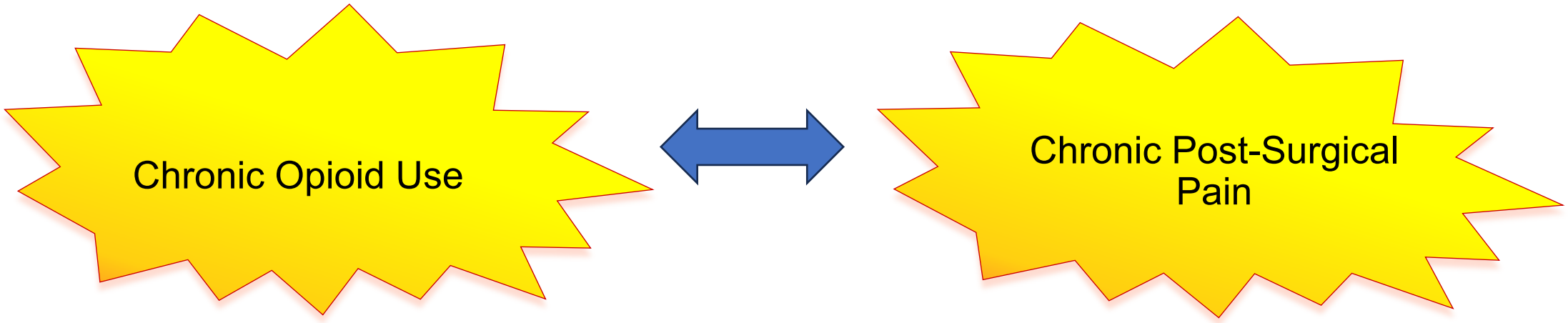
   Dichotomous vs Continuous
3. Variation in patient characteristics relevant to pain and opioid use modulation also need to be measured



- Increasing concern about routine prescription of opioids after surgery
- Proliferation of studies using administrative databases to study chronic opioid use after surgery
- Database studies often fail to capture the complexity of the perioperative experience
  - relatively low quality data
  - Often does not include relevant predictors of pain and opioid use
- The Multicenter Perioperative Outcomes Group (MPOG) is a consortium of hospitals with processes to automatically collect and extract perioperative data

Study Aims

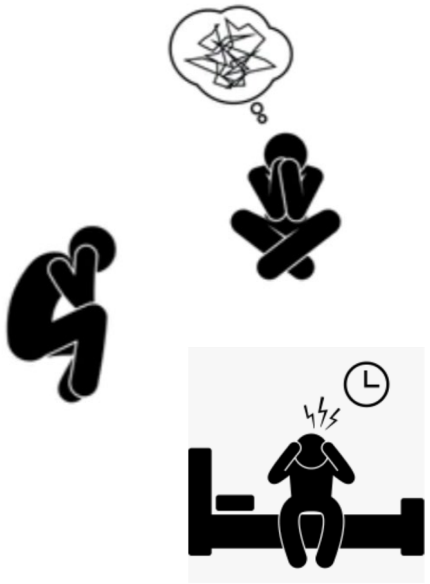
To investigate factors associated with chronic opioid use and surgical site pain at 3 months



Methods

Preoperative questionnaires

- Brief Pain Inventory, surgery site and overall
- Fibromyalgianess (Symptom Severity Index and widespread pain)
- Anxiety
- depression
- Sleep disturbance
- catastrophizing
- Physical function
- Opioid use
- expectations of surgery



Surgical factors

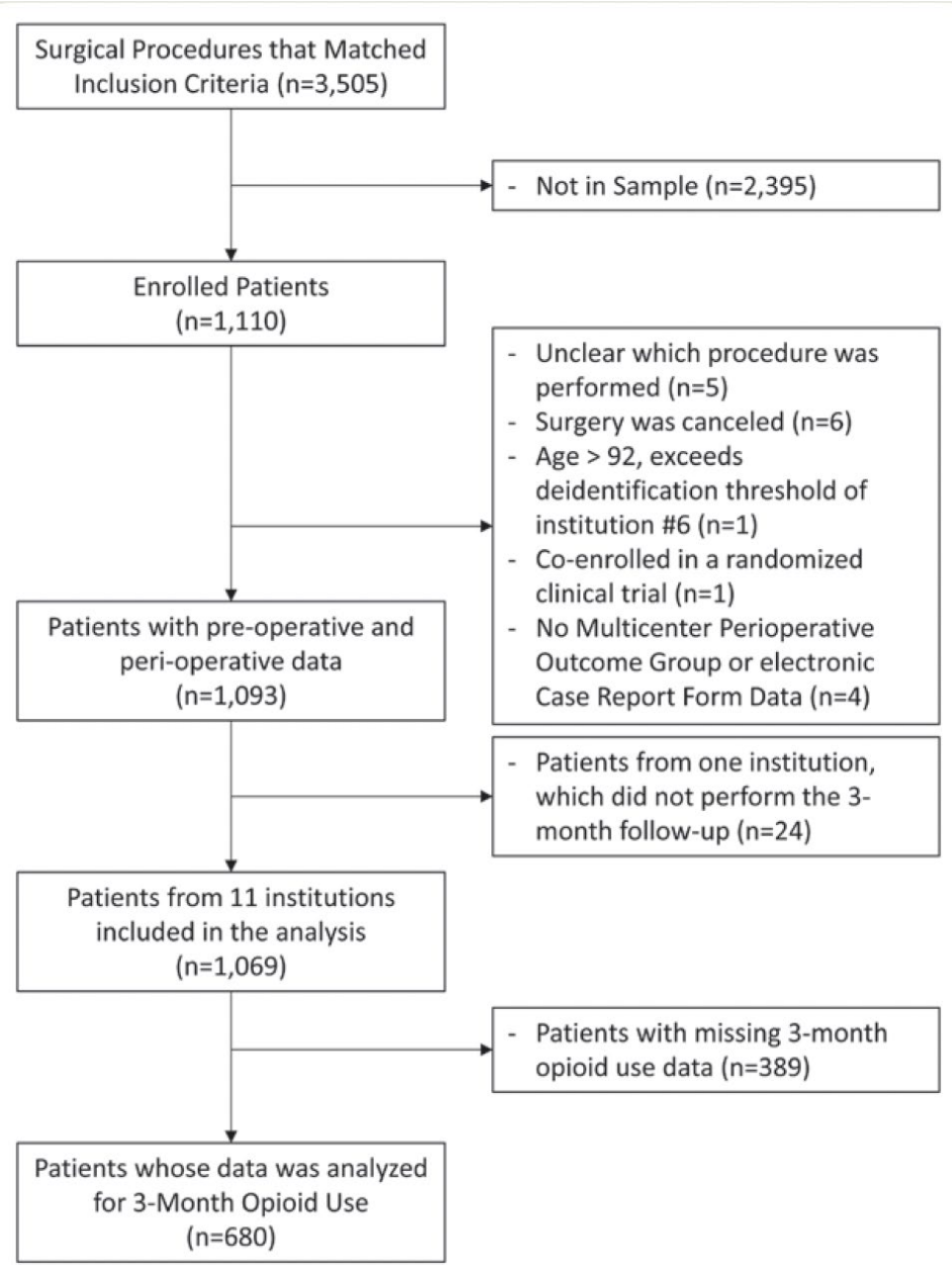
Anes factors

Chronic Opioid Use

Chronic Post-Surgical Pain

Patient sample

- September-October 2017
- 3,505 surgical procedures met inclusion criteria, with1,110 cases enrolled across 11 institutions
- completion rate of the 3-month follow-up varied between institutions:
- 7 institutions with >66% completion, remaining 62%,53%, 45%, and 34%,
- Missing outcomes were not imputed; patients with missing data were out
- Full outcome data on 680 patients



Pre- vs post-surgical opioid use

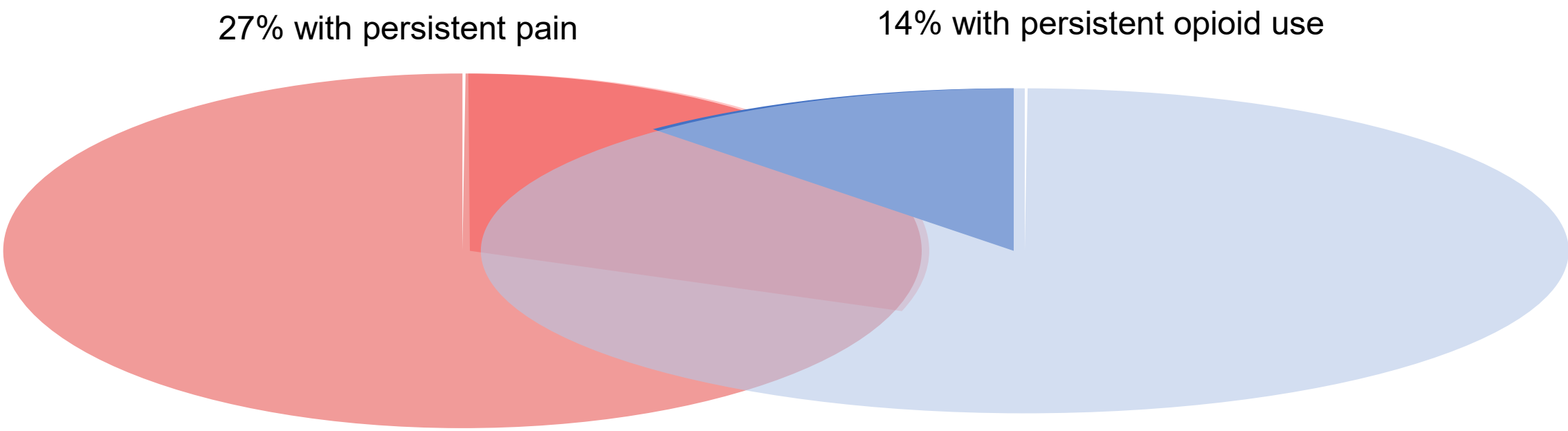
Table 3. Patients' Changes in Opioid Taking from before to 3 Months after Surgery (Based on 680 Patients for Whom 3-month Follow-ups were Completed)

BEFORE	AFTER: NO — 584 Patients Not Taking Opioids at 3 Months (86% of All Patients)	AFTER: YES — 96 Patients Taking Opioids at 3 Months (14% of All Patients)
NO	545 patients not taking opioids before surgery (80% of all patients)	522 (96% of patients not taking opioids before surgery)	23 (4% of patients not taking opioids before surgery)
YES	135 patients taking opioids before surgery (20% of all patients)	62 (46% of patients taking opioids before surgery)	73 (54% of patients taking opioids before surgery)

- only 4% of patients were "new" prolonged opioid users at 3 months
- 46% of patients stopped taking opioids

Minimal overlap of 3 month pain and opioid use

- Pain and opioid use at 3 months were not statistically associated
- unclear whether an association might have been observed if pain was considered as a continuous variable rather than dichotomous



Univariable analysis:
factors associated with pain and opioid use at 3 months

Pain at 3 mo

Opioid Use at 3 mo

Female sex

anxiety

Neuraxial anes

General anes

TKA

Spine surgery

institution

(-)employment

Preop pain

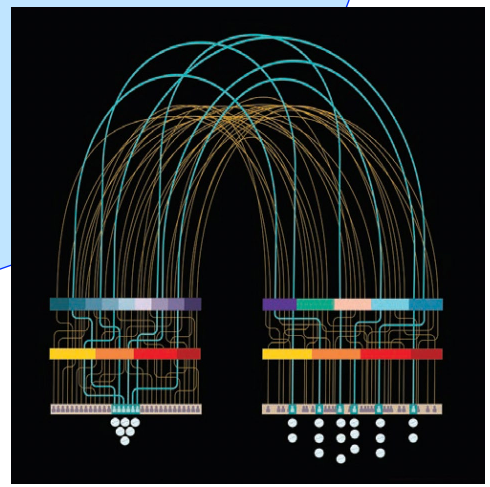
Depression

Physical function

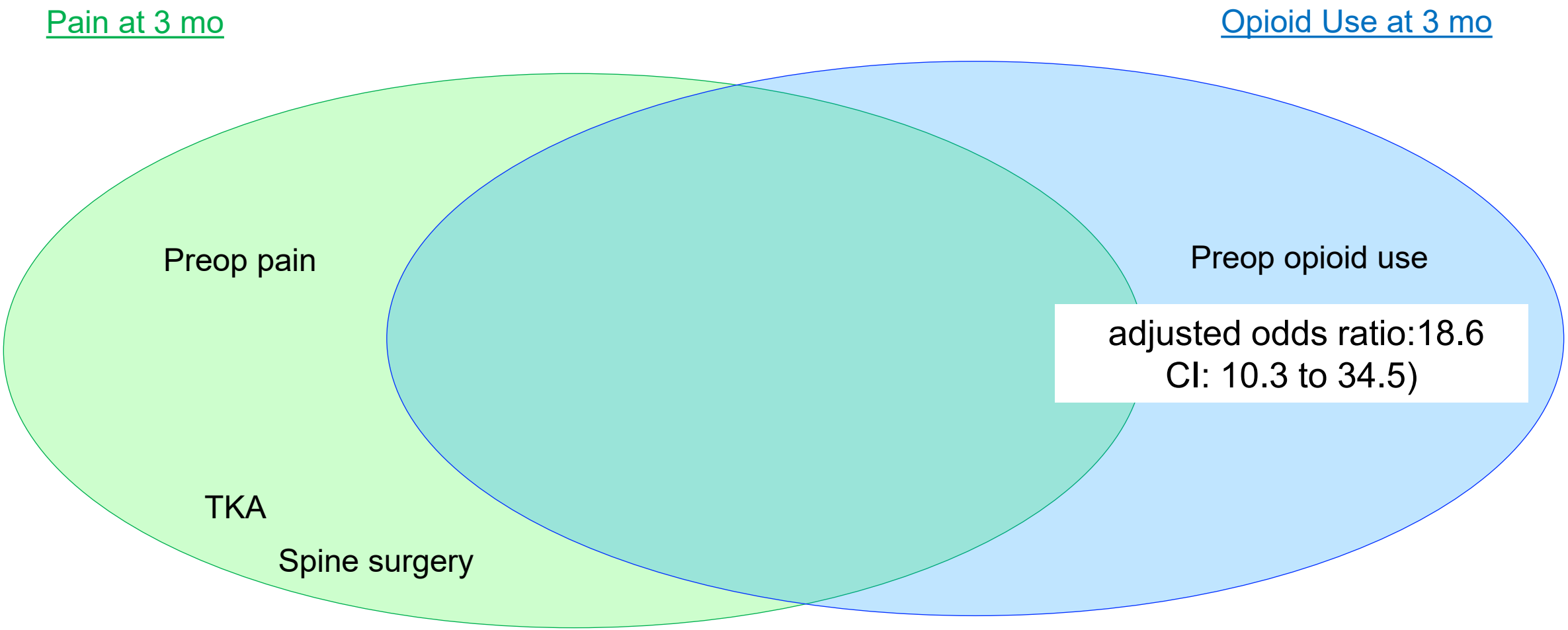
Surgery type

Preop opioid use

Intraop MME



Multivariable analysis:
factors independently associated with pain and opioid use at 3 months



Anesthesiology in 2023: Articles You Need to Know

Michael J. Avram, Ph.D.

Assistant Editor-in-Chief

FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women

(http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm)

The U.S. Food and Drug Administration (FDA) issued a change in labeling regarding the safe use of anesthetic and sedative agents in 2016. The opening sentence states that “repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains.” This warning then suggests that brief exposure is probably safe.

Exposure of Developing Brain to General Anesthesia What Is the Animal Evidence?

Vesna Jevtovic-Todorovic, M.D., Ph.D., M.B.A.

Anesthesiology 2018; 128:832 – 839

Treatment of rodents and subhuman primates with anesthetics and sedatives in utero and during early postnatal development is associated with enhanced apoptosis (neurons and glia) and alterations in neurogenesis, gene expression, cytokine expression, synaptic transmission, and lipid metabolism that are, in turn, associated with cognitive and behavioral abnormalities in later life.

Clinical Evidence for Any Effect of Anesthesia on the Developing Brain

Andrew J. Davidson, M.B.B.S., M.D., F.A.N.Z.C.A., Lena S. Sun, M.D., F.A.A.P., D.A.B.A.

Anesthesiology 2018; 128:840 – 853

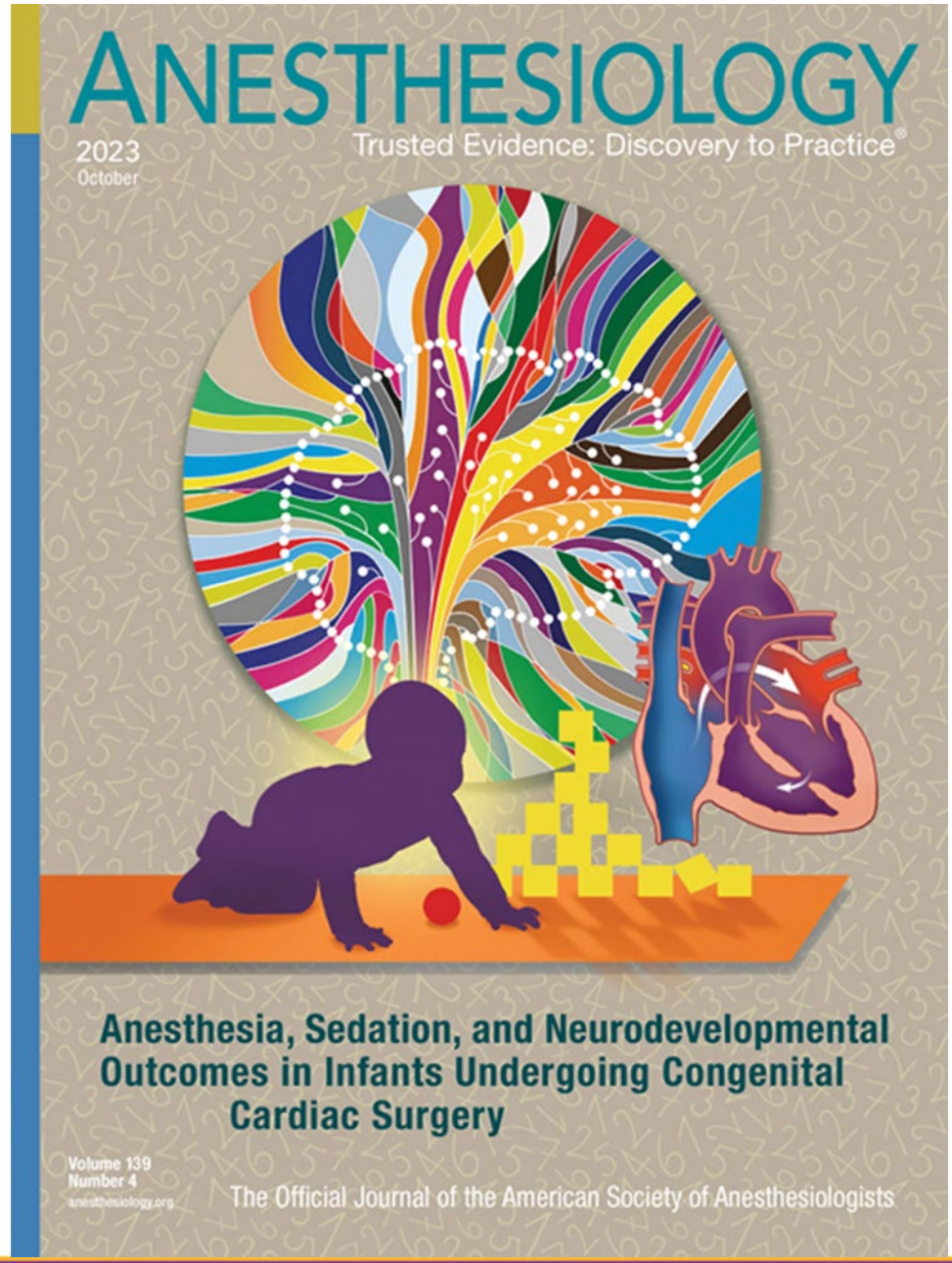
"… the human evidence for any association can only be regarded as very weak evidence that anesthesia actually causes these poorer outcomes. Thus, any recommendations for changing practice, including the FDA warning, continue to be driven largely by the preclinical evidence. In contrast, there is stronger human evidence that a single brief exposure in a healthy infant is not associated with poorer neurodevelopmental outcome."

ANESTHESIOLOGY

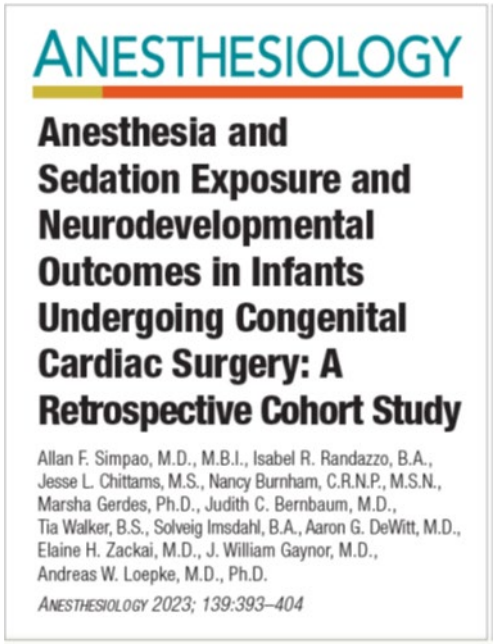
Anesthesia and Sedation Exposure and Neurodevelopmental Outcomes in Infants Undergoing Congenital Cardiac Surgery: A Retrospective Cohort Study

Allan F. Simpao, M.D., M.B.I., Isabel R. Randazzo, B.A., Jesse L. Chittams, M.S., Nancy Burnham, C.R.N.P., M.S.N., Marsha Gerdes, Ph.D., Judith C. Bernbaum, M.D., Tia Walker, B.S., Solveig Imsdahl, B.A., Aaron G. DeWitt, M.D., Elaine H. Zackai, M.D., J. William Gaynor, M.D., Andreas W. Loepke, M.D., Ph.D.

ANESTHESIOLOGY 2023; 139:393–404



Rationale


ANESTHESIOLOGY

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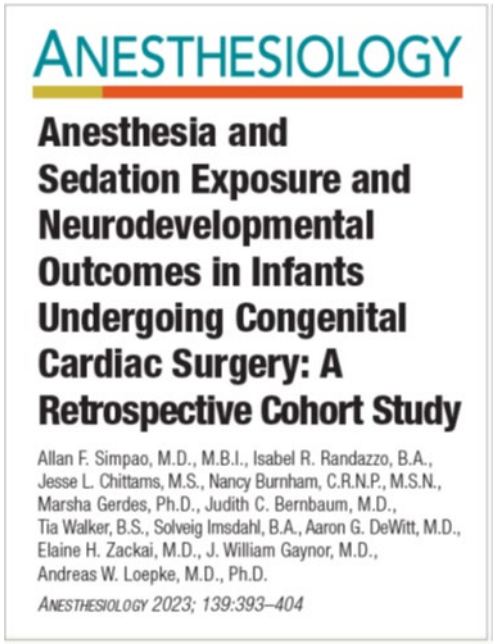
Anesthesiology 2023; 139:393–404

Children requiring cardiac surgery may be particularly susceptible to potentially deleterious effects of anesthetics and sedatives, as they frequently undergo prolonged procedures and sometimes multiple anesthetic exposures early in life, often within the neonatal period.

Hypothesis



- The hypothesis tested in a retrospective cohort study of 110 infants with congenital heart disease requiring surgery with cardiopulmonary bypass before 44 weeks post-conceptional age was that greater cumulative inpatient exposure to sedative and anesthetic medications would be associated with lower neurodevelopmental scores at 18 month follow-up.
- . The primary outcomes were the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) Motor, Language, and Cognitive scores.

Table 2. Patients Exposed to Each Medication Follow-up by Cardiac Diagnosis Class

Medication	Class I (n = 53)	Class II (n = 16)	Class III (n = 9)	Class IV (n = 32)	All Subjects (n = 110)
Fentanyl	53 (100%)	15 (94%)	9 (100%)	32 (100%)	109 (99%)
Ketamine	46 (87%)	15 (94%)	9 (100%)	31 (97%)	101 (92%)
Morphine	43 (81%)	13 (81%)	9 (100%)	32 (100%)	97 (88%)
Oxycodone	39 (74%)	5 (31%)	6 (67%)	30 (94%)	80 (73%)
Pentobarbital	26 (49%)	4 (25%)	6 (67%)	31 (97%)	67 (61%)
Midazolam	24 (45%)	6 (38%)	6 (67%)	31 (97%)	67 (61%)
Dexmedetomidine	11 (21%)	7 (44%)	8 (89%)	32 (100%)	58 (53%)
Diazepam	3 (6%)	1 (6%)	1 (11%)	6 (19%)	11 (10%)
Phenobarbital	0 (0%)	1 (6%)	0 (0.0%)	6 (19%)	7 (6%)
Propofol	6 (11%)	6 (38%)	3 (33%)	11 (34%)	26 (24%)
Lorazepam	1 (2%)	1 (6%)	0 (0.0%)	2 (6%)	4 (4%)
Meperidine	4 (8%)	1 (6%)	2 (22%)	2 (6%)	9 (8%)
Remifentanil	0 (0%)	1 (6%)	0 (0%)	0 (0%)	1 (1%)
Hydromorphone	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

The table shows the counts and percentages of patients exposed to each medication up to 18-month follow-up, by cardiac diagnosis class and total subject cohort. The cardiac diagnosis classes are defined as follows: I, two ventricles/no arch obstruction; II, two ventricles/arch obstruction; III, one ventricle/no arch obstruction; and IV, one ventricle/arch obstruction.

Table 3. Weight-adjusted Anesthetic and Sedative Exposures at 18-Month Follow-up

Anesthetic or Sedative Exposure	Units	Mean	SD	Minimum	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Maximum
Volatile anesthetic agents	MAC-h	2.4	2.5	0.0	0.1	0.6	1.6	3.4	8.2	15.0
Dexmedetomidine, perioperative	µg/kg	1.1	1.5	0.0	0.0	0.0	0.0	2.0	4.1	6.3
Opioids, perioperative and ICU	mg/kg, morphine equivalent	15.5	49.1	0.2	0.8	1.5	3.5	10.3	42.0	403.3
Benzodiazepines, perioperative and ICU	mg/kg	6.6	39.1	0.0	0.0	0.0	0.1	0.5	6.1	341.9
Dexmedetomidine, perioperative and ICU	µg/kg	8.0	12.5	0.0	0.0	0.0	1.0	12.7	35.6	65.6
Ketamine, perioperative and ICU	mg/kg	7.4	7.2	0.0	0.0	2.0	5.4	10.4	21.5	45.6

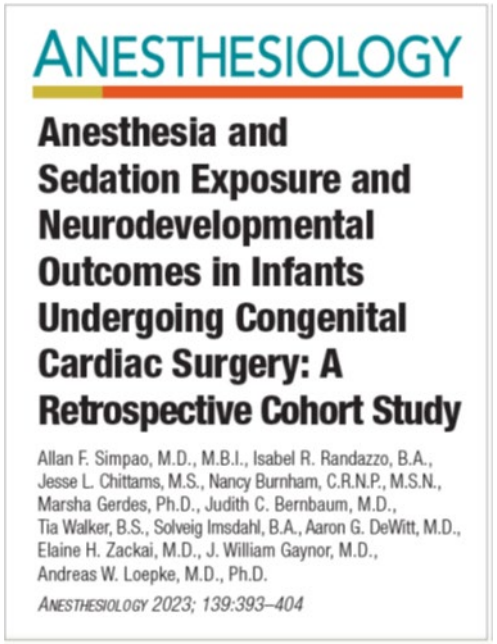
The study cohort included 110 patients. Opioids and benzodiazepines were converted to weight-adjusted intravenous morphine and midazolam equivalent doses, respectively. Volatile anesthetic agents include sevoflurane, desflurane, and isoflurane.

Table 4. Bayley Scales by Cardiac Diagnosis Class

Study Cohort Group	Bayley III Scale	Mean	SD	Minimum	25th Percentile	Median	75th Percentile	Maximum
All patients (n = 110)	Motor	92.0	11.7	52	85	94	100	118
	Cognitive	93.2	12.7	53	90	95	100	125
	Language	92.0	18.1	47	79	91	106	132
Cardiac class I or II (n = 69)	Motor	94.4	9.3	67	89	97	108	112
	Cognitive	94.3	11.1	55	90	95	100	125
	Language	93.0	18.4	47	79	91	106	132
Cardiac class III or IV (n = 41)	Motor	87.8	14.0	52	67	88	109	118
	Cognitive	91.4	14.9	53	85	95	100	120
	Language	90.2	17.7	55	77	91	106	124

The table shows the motor, cognitive, and language scores of the cohort according to the Bayley Scales of Infant and Toddler Development, 3rd edition, grouped by cardiac diagnosis class. The cardiac diagnosis classes are defined as follows: I, two ventricles/no arch obstruction; II, two ventricles/arch obstruction; III, one ventricle/no arch obstruction; and IV, one ventricle/arch obstruction.

Conclusion



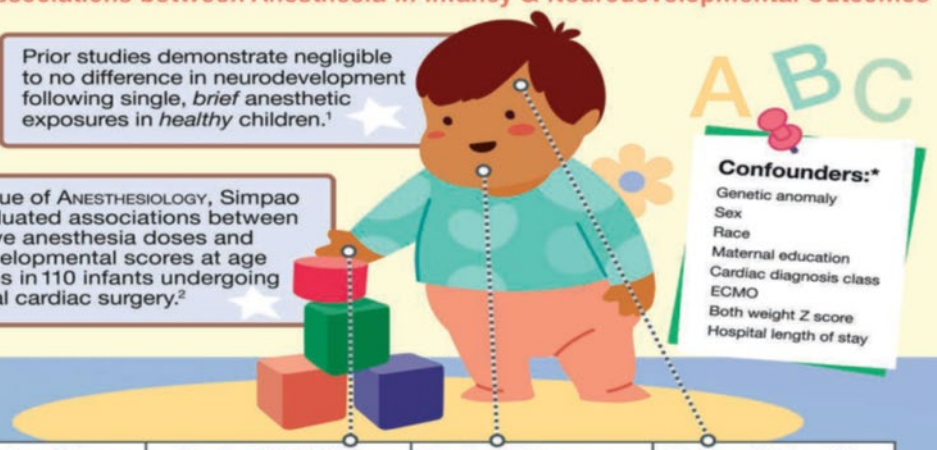
After adjusting for confounders, there were no associations between cumulative volatile anesthetic agent, opioid, benzodiazepine, and dexmedetomidine exposure up to 18-month follow-up and Bayley-III Motor, Cognitive, and Language scores but each mg/kg increase in ketamine use was associated with a 0.34-point decrease in Bayley-III Motor scores.

Debunking Developmental Delay

Assessing Associations between Anesthesia in Infancy & Neurodevelopmental Outcomes

Prior studies demonstrate negligible to no difference in neurodevelopment following single, *brief* anesthetic exposures in *healthy* children.[1]

In this issue of ANESTHESIOLOGY, Simpao *et al.* evaluated associations between cumulative anesthesia doses and neurodevelopmental scores at age 18 months in 110 infants undergoing congenital cardiac surgery.[2]



Confounders:*
- Genetic anomaly
- Sex
- Race
- Maternal education
- Cardiac diagnosis class
- ECMO
- Both weight *Z* score
- Hospital length of stay

Medication Class	Bayley III** Motor	Bayley III Language	Bayley III Cognitive
Volatile anesthetic (MAC-h)	No association β = −0.54 (−1.41, 0.32)	No association β = 0.22 (−1.18, 1.61)	No association β = −0.20 (−1.24, 0.84)
Opioids (mg/kg MME)	No association β = 0.06 (−0.03, 0.15)	No association β = 0.005 (−0.14, 0.15)	No association β = 0.02 (−0.08, 0.13)
Benzodiazepines (mg/kg)	No association β = −0.02 (−0.08, 0.04)	No association β = −0.02 (−0.11, 0.07)	No association β = 0.01 (−0.06, 0.08)
Dexmedetomidine (μg/kg)	No association β = −0.17 (−1.04, 1.15)	No association β = −0.27 (−0.57, 0.03)	No association β = −0.15 (−0.37, 0.08)
Ketamine (mg/kg)	NEGATIVE association β = −0.34 (−0.64, −0.05)	No association β = −0.07 (−0.56, 0.42)	No association β = −0.18 (−0.54, 0.19)

Conclusion: In this small, retrospective analysis, cumulative doses of volatile anesthetics and other sedative medications were not associated with neurodevelopmental impairment at age 18 months following congenital cardiac repair. However, higher ketamine doses were associated with lower motor scores.

Developmental Anesthesia Neurotoxicity: Lessons from the Heart

Caleb Ing, M.D., M.S., Laszlo Vutskits, M.D., Ph.D.
Anesthesiology 2023; 138:371 – 373

"Can we infer from (the results of this study) that prolonged administration of most anesthetics is safe in terms of neurodevelopmental outcomes? This study provides some reassurance in this regard since neither clinically meaningful nor statistically significant associations between the exposure dose of volatile anesthetics and differences in motor, cognition, or language outcomes were detected at 18 months of age. A similar lack of a dose– response was also found with opioids, benzodiazepines, and dexmedetomidine."

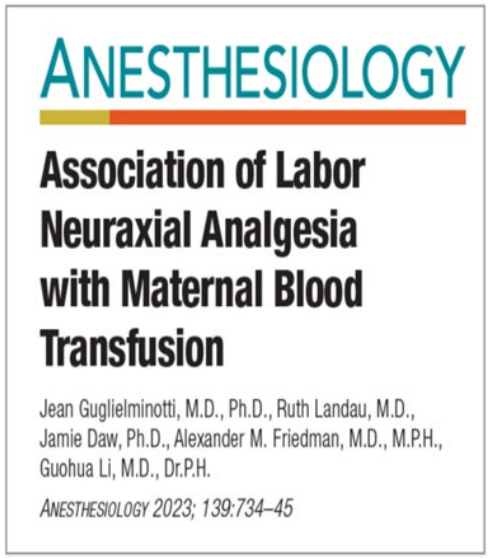
ANESTHESIOLOGY

Association of Labor Neuraxial Analgesia with Maternal Blood Transfusion

Jean Guglielminotti, M.D., Ph.D., Ruth Landau, M.D., Jamie Daw, Ph.D., Alexander M. Friedman, M.D., M.P.H., Guohua Li, M.D., Dr.P.H.

ANESTHESIOLOGY 2023; 139:734–45

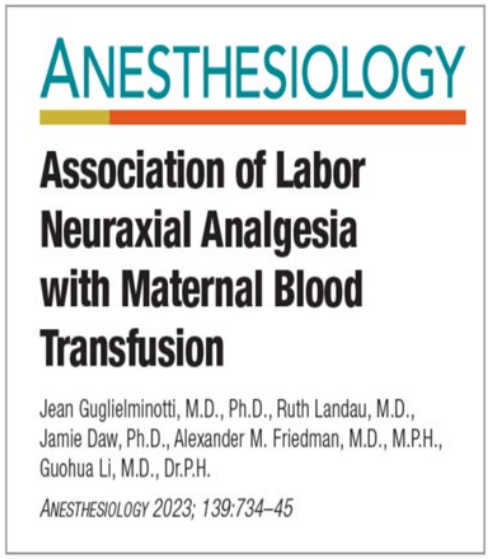
Rationale



Labor neuraxial anesthesia:

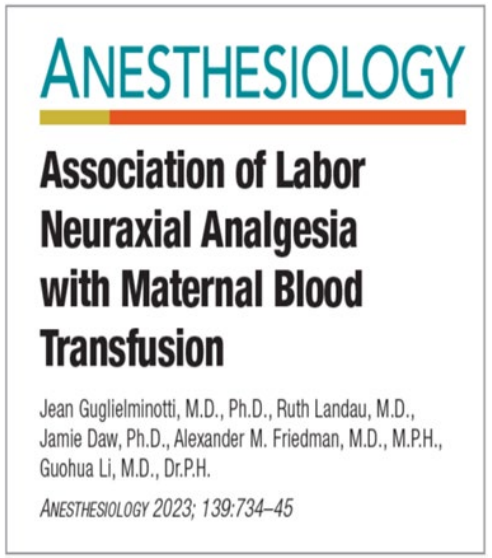
- has been associated with reduced odds of postpartum hemorrhage in women giving birth vaginally.
- may prevent use of general anesthesia, which is associated with increased odds of postpartum hemorrhage, if an intrapartum cesarean delivery is required.

Hypothesis



The hypothesis that labor neuraxial analgesia is associated with reduced odds of blood transfusion during childbirth was tested using birth certificate data for vaginal and intrapartum cesarean deliveries in the 50 states and the District of Columbia between 2015 and 2018.

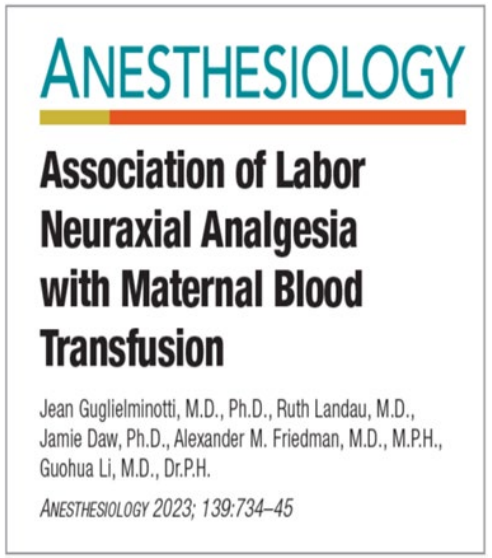
Methods - I



- Crude odds ratios of blood transfusion associated with labor neuraxial analgesia were estimated using univariate logistic regression models overall and according to delivery mode.
- As a reminder:

Odds = Probability of an Event/Probability of a Nonevent

Results - I

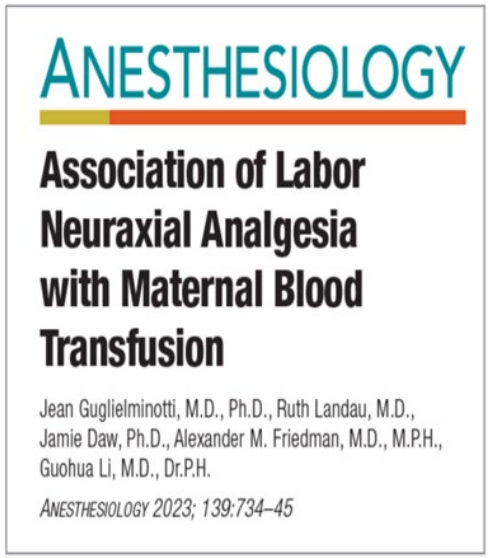


	Total	Neuraxial Analgesia	Rate
Total	12,503,042	9,479,291	75.8%
Vaginal Deliveries	9,971,031	7,180,981	72.0%
Cesarean Deliveries	2,532,011	2,298,310	90.8%

Table 3. Crude Odds Ratios of Blood Transfusion Associated with Labor Neuraxial Analgesia (United States, 2015 to 2018)

	No Labor Neuraxial Analgesia			Labor Neuraxial Analgesia				
Type of Delivery	Women, No.	Blood Transfusions, No.	Incidence per 10,000 (95% CI)	Women, No.	Blood Transfusions, No.	Incidence per 10,000 (95% CI)	Difference (Per 10,000)	Crude Odds Ratio (95% CI)
Vaginal and intrapartum cesarean deliveries	3,023,751	9,256	30.6 (30.0, 31.2)	9,479,291	33,229	35.1 (34.7, 35.4)	+4.5	1.15 (1.12, 1.17)
Vaginal deliveries	2,790,050	6,325	22.7 (22.1, 23.2)	7,180,981	16,528	23.0 (22.7, 23.4)	+0.3	1.01 (0.99, 1.04)
Intrapartum cesarean deliveries	233,701	2,931	125.4 (120.9, 130.0)	2,298,310	16,701	72.7 (71.6, 73.8)	−52.7	0.58 (0.55, 0.60)

Methods - II



WOMEN DELIVERING WITH LABOR NEURAXIAL ANALGESIA

had • a higher education level • private health insurance OR
• lived in a county with lower unemployment rate

• had gestational hypertension more often

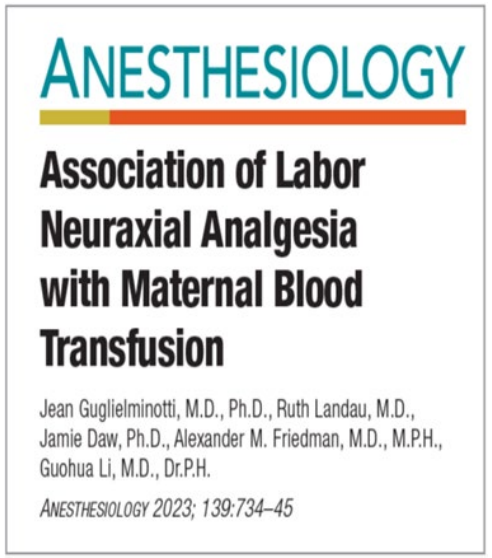
had • an earlier initiation of prenatal care OR • more prenatal visits

were more often • nulliparous OR • with a previous C-section

• had an induction or augmentation of labor

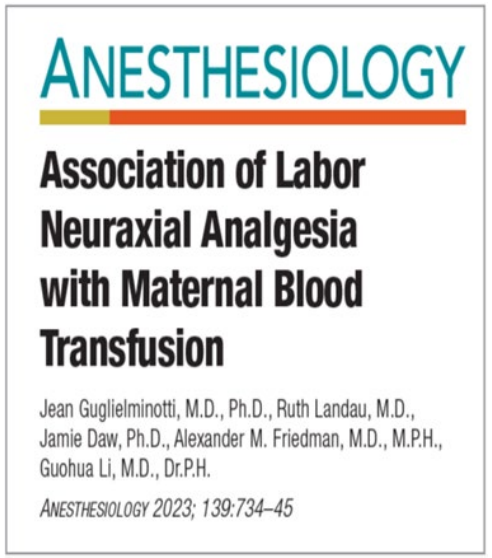
AND delivered more often
• in an urban setting OR • with a doctor of medicine as an attendant at birth

Methods - II



- Adjusted differences and adjusted odds ratios were estimated using the propensity score matching method, with the propensity score estimating the individual probability of receiving labor neuraxial analgesia.
- The propensity score was calculated using a fixed-effect logistic regression model, with labor neuraxial analgesia as the dependent variable and 33 patient- and hospital-level characteristics as the independent variables.
- Adjusted odds ratios were estimated using conditional logistic regression models, overall and by delivery mode.

Results - II



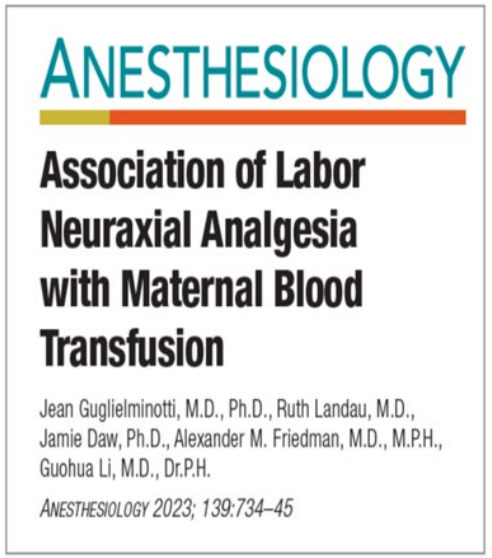
	Total	Neuraxial Analgesia	Rate
Total	5,178,986	2,589,493	50%
Vaginal Deliveries	4,756,932	2,378,466	50%
Cesarean Deliveries	422,054	211,027	50%

Table 4. Adjusted Odds Ratios of Blood Transfusion Associated with Labor Neuraxial Analgesia Using the Propensity Score Matching Method (United States, 2015 to 2018)

	No Labor Neuraxial Analgesia			Labor Neuraxial Analgesia					
Type of Delivery	Women, No.	Blood Transfusions, No.	Incidence per 10,000 (95% CI)	Women, No.	Blood Transfusions, No.	Incidence per 10,000 (95% CI)	Difference per 10,000	Adjusted Odds Ratio (95% CI)*	E Value†
Vaginal and intrapartum cesarean deliveries	2,589,493	7,907	30.5 (29.9, 31.2)	2,589,493	5,225	20.2 (19.6, 20.7)	−10.4	0.87 (0.82, 0.91)	1.56
Vaginal deliveries	2,378,466	5,282	22.2 (21.6, 22.8)	2,378,466	4,039	17.0 (16.5, 17.5)	−5.2	0.93 (0.88, 0.98)	1.36
Intrapartum cesarean deliveries	211,027	2,625	124.4 (119.7, 129.2)	211,027	1,186	56.2 (53.1, 59.5)	−68.2	0.55 (0.48, 0.64)	3.04

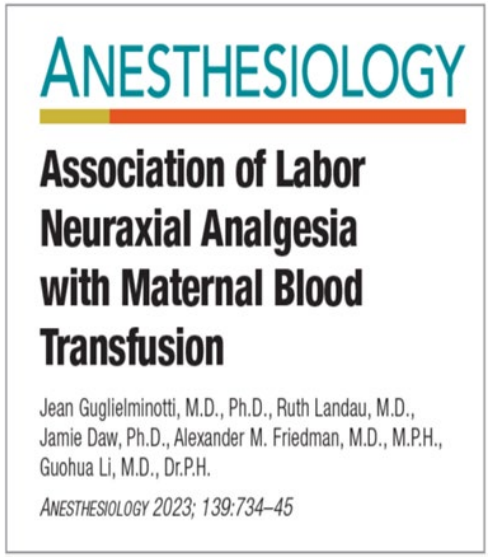
*Estimated in propensity score matched data using a conditional logistic regression and further adjustment for three variables with a persistent imbalance after matching: (1) hospital county number of in-hospital births, (2) hospital county number of certified registered nurse anesthetists, and (3) hospital state. †The E value estimates how strong an unmeasured confounder would need to be to explain away the observed association between labor neuraxial analgesia and blood transfusion, conditional of the measured covariates. The lowest possible E value is 1 and indicates that no unmeasured confounding is needed to explain away the observed association. The higher the E value, the stronger the confounder association must be to explain away the observed association.

Conclusion



"In this national study of vaginal and intrapartum cesarean deliveries, labor neuraxial analgesia was associated with reduced odds of maternal blood transfusion, … Reduction in the odds of maternal blood transfusion was more pronounced in intrapartum cesarean deliveries than in vaginal deliveries (45% vs. 7%). … The small effect size for vaginal deliveries raises legitimate concern about its clinical relevance and reproducibility."

Caveat



"We cannot rule out with certainty mechanisms other than labor neuraxial analgesia per se that are responsible for the observed reduced odds of maternal blood transfusion. … use of labor neuraxial analgesia could be a proxy for provision of high-quality obstetric anesthesia care."

Embracing Labor Neuraxial Analgesia as a Tool to Reduce Health Inequities and Hemorrhage-related Maternal Morbidity

Melissa E. Bauer, D.O., Lindsay K. Admon, M.D.

Anesthesiology 2023; 139:717–8

"The authors' data support what many obstetric anesthesiologists have long suspected: patients receiving neuraxial analgesia during labor may have reduced odds of receiving a blood transfusion, particularly patients ultimately needing a cesarean delivery."

Table 1. Labor Neuraxial Analgesia Rate According to Maternal Race and Ethnicity (United States, 2015 to 2018)

Population	Number of Women	Number of Women with Labor Neuraxial analgesia	Labor Neuraxial Analgesia Rate (95% CI)
All women	12,503,042	9,479,291	75.82% (75.79 to 75.84)
Non-Hispanic White	6,506,786	5,128,373	78.82% (78.78 to 78.85)
More than one race	271,959	209,126	76.90% (76.74 to 77.05)
Asian and Pacific Islander	851,063	650,659	76.45% (76.36 to 76.54)
Non-Hispanic Black	1,801,365	1,354,148	75.17% (75.11 to 75.24)
Hispanic	2,971,883	2,074,383	69.80% (69.75 to 69.85)
Native American	99,986	62,602	62.61% (62.31 to 62.91)

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"Considering this potential transfusion avoidance benefit of labor neuraxial analgesia, equitable efforts should be undertaken to make the provision of labor neuraxial analgesia accessible to all who desire it. Inequities persist regarding which patients receive labor neuraxial analgesia. ... Only through continuously re-evaluating the barriers, engaging with patients and surrounding communities, and creating strategies to address barriers will we begin to address inequities in care."

2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade: A Report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade

Stephan R. Thilen, M.D., M.S. (co-chair),
Wade A. Weigel, M.D. (co-chair), Michael M. Todd, M.D.,
Richard P. Dutton, M.D., M.B.A., Cynthia A. Lien, M.D.,
Stuart A. Grant, M.D.,
Joseph W. Szokol, M.D., J.D., M.B.A., FASA,
Lars I. Eriksson, M.D., Ph.D., FRCA,
Myron Yaster, M.D., Mark D. Grant, M.D., Ph.D.,
Madhulika Agarkar, M.P.H., Anne M. Marbella, M.S.,
Jaime F. Blanck, M.L.I.S., M.P.A.,
Karen B. Domino, M.D., M.P.H.

ANESTHESIOLOGY 2023; 138:13–41

The 2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade

- Recommend using quantitative neuromuscular monitoring at the adductor pollicis muscle and confirming recovery of train-of-four ratio ≥ 0.9 prior to extubation.
- Recommend using sugammadex for reversal of deep, moderate, and shallow levels of neuromuscular blockade that is induced by rocuronium or vecuronium.
- Suggest neostigmine is an alternative to sugammadex for antagonism of minimal neuromuscular blockade (train-of-four ratio in the range 0.4 to < 0.9).
- Indicate patients with spontaneous recovery to train-of-four ratio ≥ 0.9 identified with quantitative neuromuscular monitoring do not require pharmacological antagonism.
- Discuss methods for implementing routine quantitative monitoring for patients receiving neuromuscular blocking agents.

Measuring Success of Patient Safety Initiatives: The 2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade

Sorin J. Brull, M.D., F.C.A.R.C.S.I. (Hon), Aaron Kopman, M.D.

Anesthesiology 2023; 138:4–6

"[These practice guidelines...] should represent the basis for a consensus on safe administration and reversal of neuromuscular blocking drugs in daily practice."

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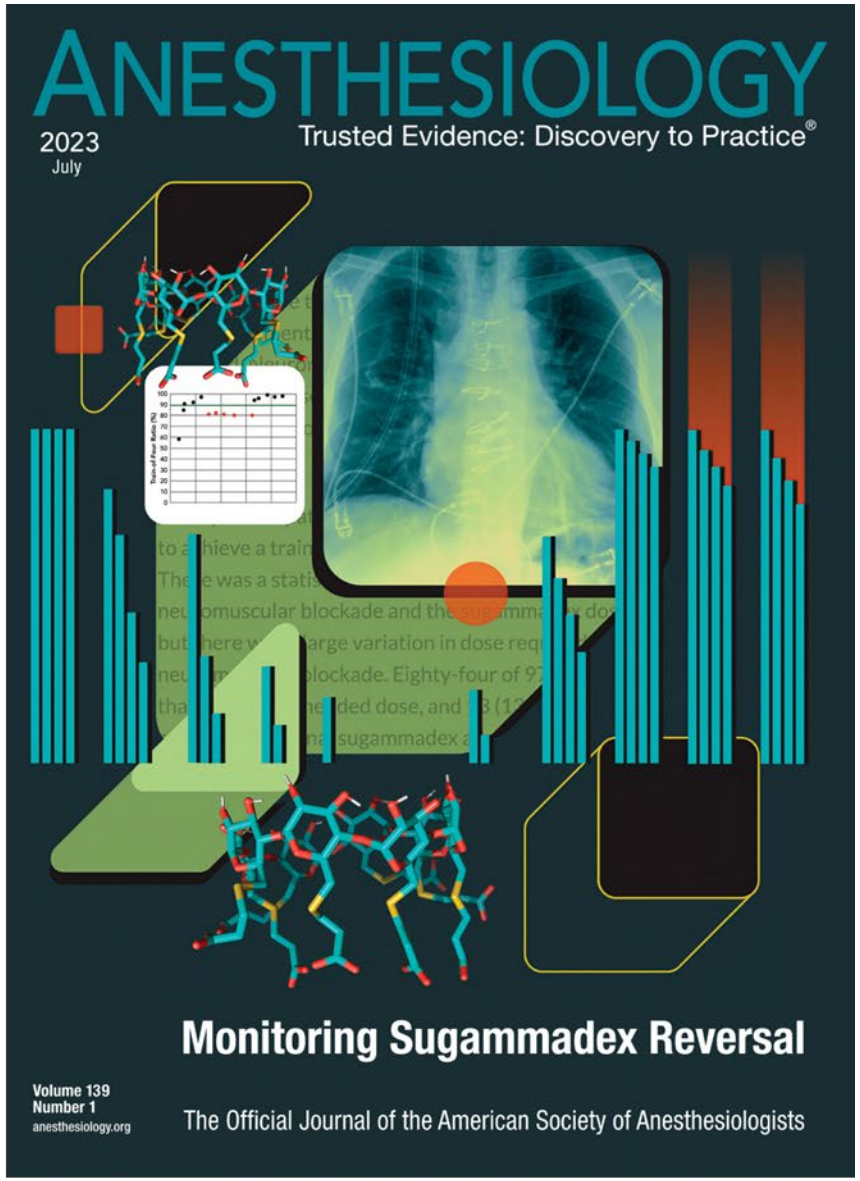
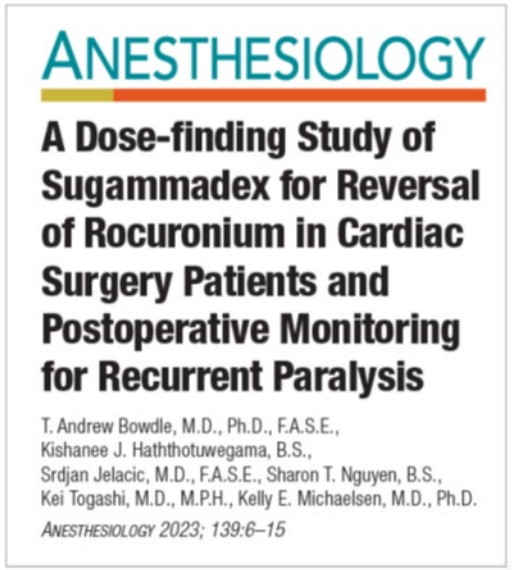
A Dose-finding Study of Sugammadex for Reversal of Rocuronium in Cardiac Surgery Patients and Postoperative Monitoring for Recurrent Paralysis

T. Andrew Bowdle, M.D., Ph.D., F.A.S.E.,
Kishanee J. Haththotuwegama, B.S.,
Srdjan Jelacic, M.D., F.A.S.E., Sharon T. Nguyen, B.S.,
Kei Togashi, M.D., M.P.H., Kelly E. Michaelsen, M.D., Ph.D.

ANESTHESIOLOGY 2023; 139:6–15

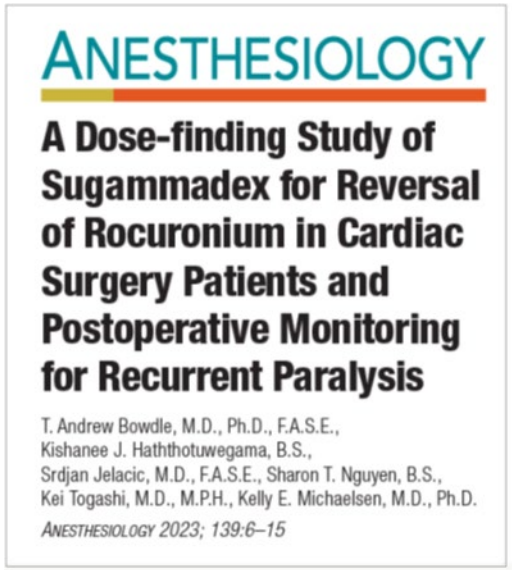


Sugammadex



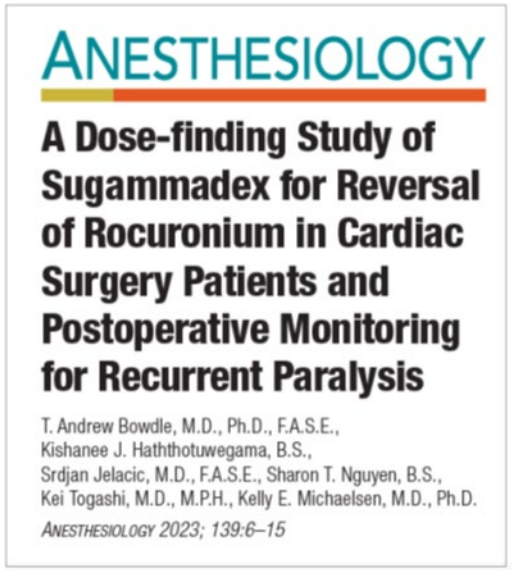
- Sugammadex is effective for reversing neuromuscular blockade produced by rocuronium or vecuronium.
- The manufacturer has recommended that a sugammadex dose of 2 mg/kg be administered if at least two twitches are present in response to a train-of-four stimulus, or 4 mg/kg if there are less than two twitches but a post-tetanic count of more than 0.

Hypothesis



The hypothesis that many patients would require less than the recommended dose of sugammadex, but that some would require more, and that recurrent paralysis would not occur was tested in a prospective dose-finding study of 97 cardiac surgery patients administered rocuronium in whom neuromuscular blockade was monitored using an electromyography-based twitch monitor.

Methods



- Sugammadex was titrated in 50 mg increments every 5 min until a train-of-four ratio of at least 0.9 was reached at the conclusion of cardiac surgery.
- Quantitative twitch monitoring was continued postoperatively in the ICU while the patients remained sedated and intubated.

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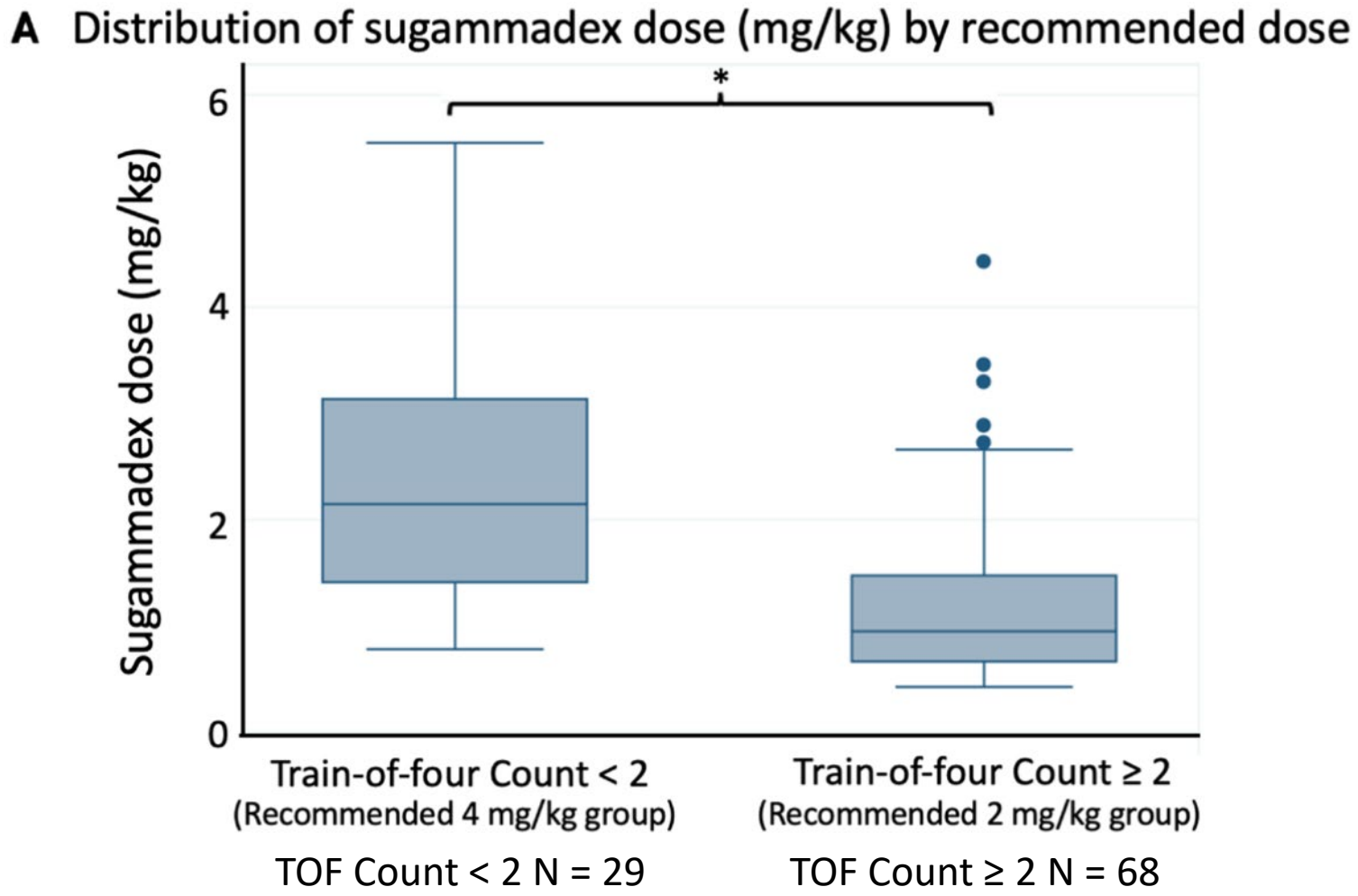
ANESTHESIOLOGY 2023; 139:6–15



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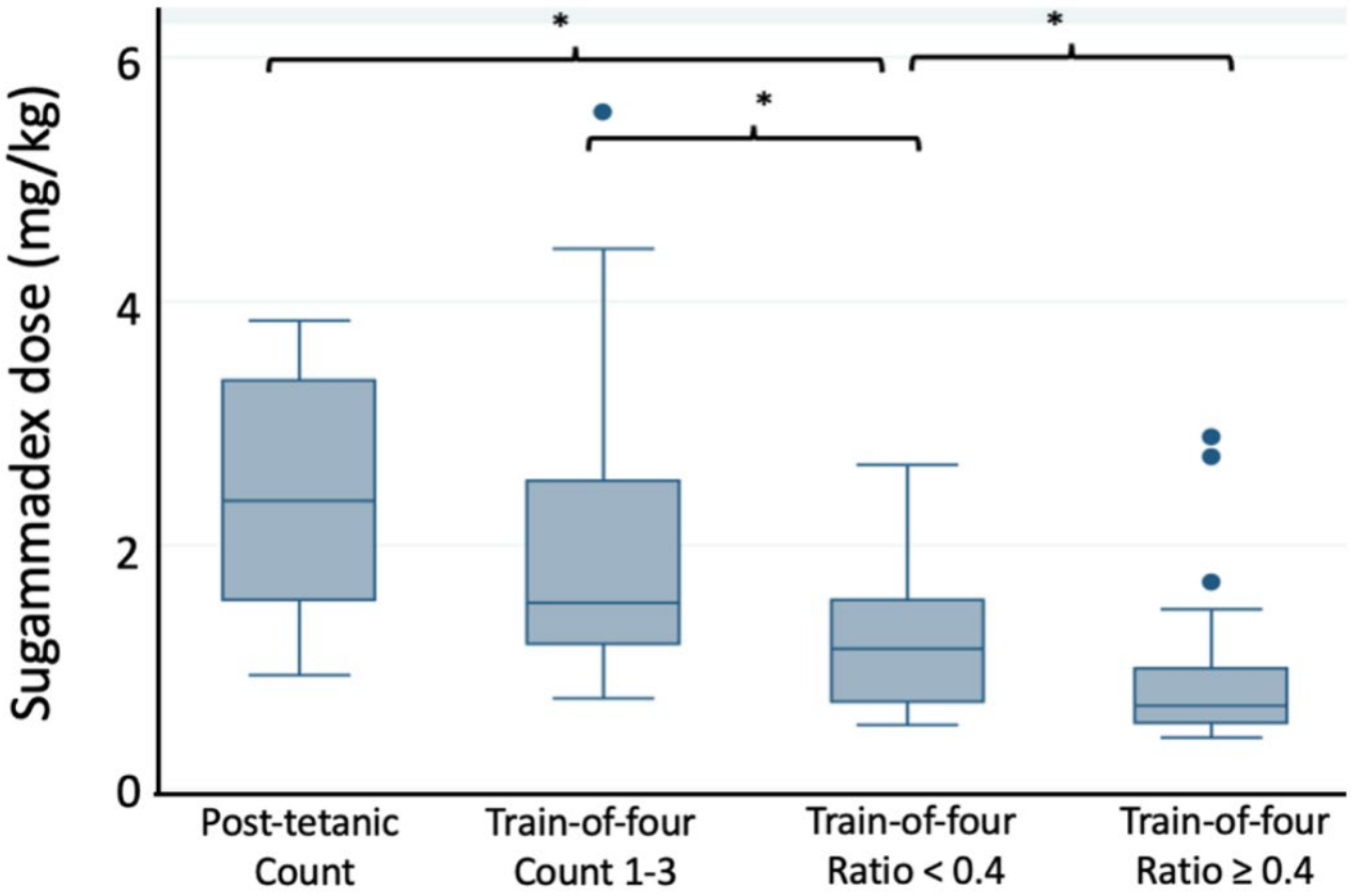
B Distribution of sugammadex dose (mg/kg) by twitch response



Two Subjects with Recurrent Paralysis

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A Dose-finding Study of Sugammadex for Reversal of Rocuronium in Cardiac Surgery Patients and Postoperative Monitoring for Recurrent Paralysis

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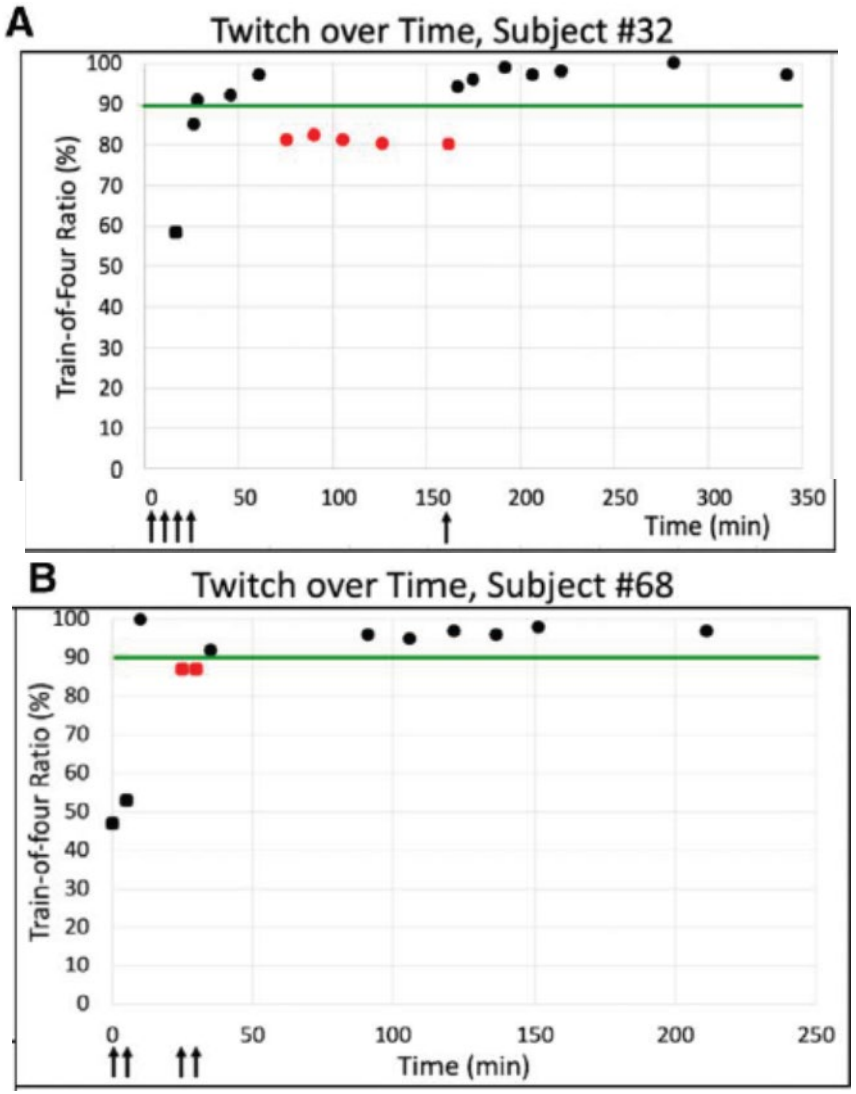
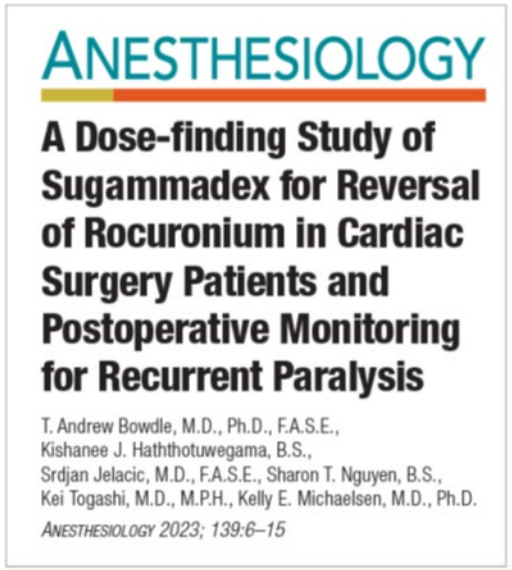
Anesthesiology 2023; 139:6–15



Conclusions



- The range of dose requirements for patients with the same twitch response varied greatly. Eighty-four of 97 patients (87%) required less than the manufacturer's recommended dose and 13 (13%) required more.
- Since the dose required could not be predicted with certainty based on the train-of-four twitch response immediately before reversal, quantitative twitch monitoring is essential to evaluate the effectiveness of reversal with sugammadex.

Goldilocks and the three Rocuronium Reversals:

A Sugammadex Dose-finding Study

The manufacturer-recommended dose of sugammadex for reversal of rocuronium is:

- **2 mg/kg** when train-of-four (TOF) count is ≥2
- **4 mg/kg** when the TOF count is <2 with posttetanic count ≥1

In the current study, Bowdle *et al.* used electromyography to monitor recovery from rocuronium-induced neuromuscular blockade after cardiac surgery. Sugammadex was titrated in 50-mg increments every 5 min until a TOF ratio ≥0.9 was obtained.[1]

97 Patients Evaluated

Sugammadex dose to achieve TOF ratio ≥0.9 ranged from 0.43-5.6 mg/kg

TOF count ≥2 (n=68)

Mean sugammadex dose requirement = 1.24 (SD 0.83) mg/kg *(less than recommended 2 mg/kg)*

11 of 68 (16%) required more than 2 mg/kg to achieve TOF ratio ≥0.9

TOF count <2 (n=29)

Mean sugammadex dose requirement = 2.30 (SD 1.18) mg/kg *(less than recommended 4 mg/kg)*

2 of 29 (7%) required more than 4 mg/kg to achieve TOF ratio ≥0.9

Too Much

84 of 97 (87%) patients did not require the full recommended dose to achieve TOF ≥ 0.9

Too Little

13 of 97 (13%) patients required more than the recommended dose

Just Right

To get the dose just right, quantitative TOF monitoring is strongly recommended

CONCLUSION: While many patients required less than the recommended sugammadex dose to reverse neuromuscular blockade with rocuronium, some required more. Quantitative twitch monitoring is essential to confirm adequate reversal.

Sugammadex Is Not a Silver Bullet: Caveats Regarding Unmonitored Reversal

Michael M. Todd, M.D., Aaron F. Kopman, M.D.

Anesthesiology 2023; 139:1 – 3

"This work contains a number of findings that deserve attention from our entire profession. Most importantly, it contradicts the widespread belief that simply giving the recommended 2- or 4-mg/kg dose of sugammadex, based solely on an observed twitch count (or post-tetanic count) ensures adequate reversal. … the … study strongly argues that the recommendations should be combined with careful monitoring."

Sugammadex Is Not a Silver Bullet: Caveats Regarding Unmonitored Reversal

Michael M. Todd, M.D., Aaron F. Kopman, M.D.

Anesthesiology 2023; 139:1 – 3

"… at an EMG train-of-four ratio of 0.90, while a subject may have few symptoms of residual block, his/her neuromuscular reserve is still markedly diminished. This may be of little consequence in young, healthy patients, but in our sickest and oldest patients having major surgery, we should probably consider a target value closer to 1.0 with any form of quantitative monitoring."

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