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Variation in propofol induction doses administered to surgical patients over age 65

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Abstract

Background/Objectives: Advanced age is associated with increased susceptibility to acute adverse effects of propofol. The present study aimed to describe patterns of propofol dosing for induction of general anesthesia before endotracheal intubation in a nationwide sample of older adults presenting for surgery.

Design: Retrospective observational study using the Multicenter Perioperative Outcomes Group data set.

Setting: Thirty-six institutions across the United States.

Participants: A total of 350,766 patients aged over 65 years who received propofol for general anesthetic induction and endotracheal intubation between 2014 and 2018.

Intervention: None.

Measurements: Total induction bolus dose of propofol administered.

Results: The mean (SD) weight-adjusted propofol dose was 1.7 (0.6) mg/kg. The mean prevalent propofol induction dose exceeded the upper bound of what has been described as the typical geriatric dose requirement across every age category examined. The percent of patients receiving propofol induction doses above the described typical geriatric range was 64.8% (95% CI 64.6–65.0), varying from 73.8% among patients aged 65–69 to 45.8% among patients aged 80 and older.

Conclusion: The present study of a large multicenter cohort demonstrates that prevalent propofol dosing commonly falls above the published typically required dose range for patients aged ≥65 in nationwide anesthetic practice. Widespread variability in induction dose administration remains incompletely explained by known patient variables. The nature and clinical consequences of these unexplained dosing decisions remain important topics for further study.

See related editorial by Devinney et al. in this issue.

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Observed discordance between expected and actual induction dosing raises the question of whether there should be reconsideration of widespread provider practice or, alternatively, whether what is published as the typical propofol induction dose range should be revisited.

KEYWORDS

anesthetic induction, geriatric dosing, propofol

1 | INTRODUCTION

The U.S. population is aging, with over 16.5% of Americans now over age 65.[1] Older patients account for approximately 40% of the surgical procedures performed each year.[2] Older patients undergoing surgical procedures often have age-related medical conditions and frailty,[3-6] which increase risks of adverse outcomes.[7,8] In addition to the greater medical morbidity that accompanies aging,[9,10] physiologic changes in metabolism and end-organ function that accompany aging increase the effective potency of anesthetic agents. Propofol sensitivity is increased by approximately 30% to 50% in the elderly compared with younger patients.[11] Even among relatively healthy elderly patients treated under controlled, experimental conditions, advanced age is associated with substantially increased susceptibility to acute adverse effects of propofol.[12]

In recognition of the adverse consequences of advanced age on anesthetic potency, the Food and Drug Administration (FDA)-approved package insert for propofol recommends adjusting the general anesthesia induction dose among patients aged >55 years to 1–1.5 mg/kg as opposed to the 2–2.5 mg/kg recommendation for patients under 55 years of age. Consistent with this recommendation, among generally healthy people aged 60–75 years who presented for elective outpatient surgery, Electroencephalogram (EEG)-guided general anesthetic states sufficient for endotracheal intubation were reliably induced following a mean propofol dose of 1.27 mg/kg.[13] Despite product label guidance and empirical evidence regarding typical dose requirements for geriatric populations, small, single-center cohort studies[14-16] suggest that prevalent dosing often exceeds the expected typical dose range. Other studies have documented elevated dosing of inhalation agents for older adults during the maintenance period of anesthetics relative to what literature would seem to recommend.[17,18] Beyond these single-center reports, large, population-based studies of prevalent propofol induction dosing practices for geriatric surgical patients have not been described.

It is well-recognized that doses required by individual patients, or even by the same patient, may vary based on a variety of context-specific factors. Thus, an analysis of actual propofol induction dosing practice among older adults—and how such practice relates to what is deemed by approved labeling to be the typically required range—may generate questions regarding whether current labeling or current practice patterns may be in need of further investigation.

Using a sample of adults aged 65 years and older derived from the Multicenter Perioperative Outcomes Group (MPOG), we describe population-based patterns

Key Points

- In a nationwide sample of propofol induction dosing practices for patients aged over 65 years undergoing general anesthesia, almost two-thirds of administered doses were discordant with published typical dose requirements for this age group.
- Variation in prevalent propofol induction dosing across institutions is not explained solely by differences in patient populations.
- The range of propofol induction doses commonly used in modern anesthetic practice is broad and is not fully explained by demographic and comorbidity variables available in the present dataset. Future investigations should endeavor to understand the nature of these highly variable dosing decisions and how such dosing may relate to important clinical outcomes.

Why Does this Paper Matter?

This multicenter investigation demonstrates discordance between clinical practices and the expected typical dose range for propofol induction in older adults. It is a key step in the ongoing effort to identify opportunities to improve anesthetic care of older adults.

and predictors of propofol induction dosing practices for geriatric surgical patients. MPOG is a consortium of over 50 academic and community hospitals dedicated to sharing data for quality improvement and research in anesthesiology.[19-21]

Our objective was to describe prevalent propofol induction dosing patterns. Our primary inferential hypothesis was that prevalent propofol induction dosing among patients aged 65 years and older would exceed the described typical dose range in more than 30% of cases, consistent with prior observational data. Specific analyses sought to (a) delineate patterns of weight-adjusted propofol induction dose by age and severity of illness; (b) examine predictors of and variation in prevalent propofol dose across patient, institutional, and surgical factors; and (c) examine the extent of discontinuous propofol induction dosing at 50 mg increments.

2 | METHODS

This was a retrospective observational study conducted under an approved IRB protocol in collaboration with the MPOG.[22,23] MPOG is a consortium of over 50 hospitals that maintain a data set of electronic health record (EHR) and administrative data from contributing sites across 21 states and two countries. The MPOG data collection methods have been previously described (see www.mpog.org).[19,20] Briefly, MPOG-contributing sites conduct automated extraction of perioperative data including patient and procedural characteristics, anesthetic medications, physiologic parameters, and key surgical events.

Contributing sites conduct monthly case-by-case validation of a random sample of submitted data by subject-matter experts. The MPOG Perioperative Clinical Research Committee approved the use of data for this project, and the analytic plan for the present analyses was publicly registered on the website of the Open Science Framework with modifications as noted in the manuscript. The study was conducted in accordance with the Reporting of studies Conducted using Observational Routinely–collected health Data (RECORD) statement, an extension of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[24,25]

Surgical cases of patients aged ≥65 years who underwent induction of general anesthesia including propofol bolus dosing before endotracheal intubation between January 2014 and December 2018 were identified. Only data from centers with consistent data uploads and case validation were included. For patients who underwent multiple anesthetics in the study period, only the index case was included.

Patients were excluded if they were designated as American Society of Anesthesiologists Physical Status (ASA PS) 5 or 6,[26,27] indicating a moribund or brain-dead patient, respectively. Cases were excluded if the patient a) arrived to the operating room already intubated or b) presented with hemodynamic derangements including severe hypertension or hypotension. Hypertensive patients were excluded for mean arterial pressure (MAP) > 135 mmHg or diastolic blood pressure > 110 mmHg. Hypotensive patients were excluded for MAP <55 mmHg or systolic blood pressure < 90 mmHg. Patients receiving anesthetics for minor procedures as determined by the base unit value of anesthesia billing less than or equal to 3 were excluded. Patients who did not undergo endotracheal intubation were excluded. Finally, patients with missing or outlier propofol induction dosing or with other missing or outlier variables were excluded by investigator consensus.

For the selected sample, extracted data comprised demographic variables (age, sex, race/ethnicity, anonymized institution ID, and year of surgery) and patient-level clinical characteristics (weight, height, body mass index categorized into the World Health Organization obesity classifications,[28] ASA PS, preoperative mean arterial pressure, the presence of coronary artery disease, and Elixhauser comorbidity status[29]). Data sources for patient and surgical characteristics relied on MPOG-validated, publicly available perioperative EHR phenotype algorithms.[30] Elixhauser comorbidities were combined into a single comorbidity index based on the van Walraven modification of the Elixhauser classifications.[31] The van Walraven–Elixhauser comorbidity score is a weighted index created from among 30 comorbid conditions that have been demonstrated to independently predict hospital mortality with superior discrimination in comparison to the Charlson Comorbidity Index.[32] Administrative codes were also queried to calculate an index of the likelihood of frailty.[4]

Where laboratory data were available, preoperative albumin level, preoperative hemoglobin levels, and estimated glomerular filtration rate (eGFR) were included. eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi)[33] or using the Cockcroft–Gault formula[34] if race was missing.[35] The eGFR was coded into chronic kidney disease stages in accordance with prior literature.[36]

Surgeries were classified by the specialty of the primary proceduralist and the presence or absence of an emergency modifier in the ASA PS classification. Institutions were classified as academic versus community based on the presence of an affiliation with a medical school. Classifications of providers within institutions (e.g., solo anesthesiologist, supervised nurse, or supervised resident) were highly imbalanced across institutions and thus were not considered for analysis.

Intraoperative records were queried to calculate the total bolus intravenous anesthetic doses delivered within 15 min of induction but ending at surgical incision. In addition to propofol, intravenous anesthetics recorded for the analysis included midazolam, fentanyl, etomidate, ketamine, methohexital, and thiopental. If neuraxial anesthetics (i.e., epidural or spinal anesthetics) were administered concomitantly, this was recorded as a categorical variable. As the present manuscript was aimed at delineating contemporary propofol induction dosing practices, postinduction intraoperative data were not examined.

2.1 | Statistical analysis

Following delineation of the cohort, descriptive statistics (means, standard deviations (SDs), medians, interquartile ranges, and frequencies) were computed as relevant.

Cleaning of data: In addition to contributing-site data validation, study-specific data were examined for outlier values, which were considered in relation to clinical plausibility with cutpoints derived by agreement among investigators. Missingness was examined for each variable. In accordance with the *a priori* plan, the albumin level demonstrated greater than 40% missingness and was removed from consideration.

2.2 | Propofol induction dose by age and ASA PS

After initial assessment of data quality and distributions, propofol induction dosing was summarized in relation to what the FDA-approved package insert describes as the typical dosing range across four age subgroups (65–69 years, 70–74 years, 75–79 years, and ≥80 years) and within four categories of comorbidity status (ASA PS 1, 2, 3, and 4) for a total of 16 age by severity of illness subcategories. Within each subcategory, mean, SD of propofol dose, and percent dose in excess of the described typical dosing range (i.e., >1.5 mg/kg) were calculated.

2.3 | Independent predictors of propofol induction dose

To determine predictors of propofol induction dose and derive the adjusted rates of doses in excess of the package insert's listed typical dose requirement, we fit suitable hierarchical logistic regression models that accounted for the clustering of the data within institutions to (1) identify covariates (fixed effects) including patient, institutional, and surgical characteristics that were significantly associated with excess prevalent dose; (2) predict the random effects of institutions after adjusting for significant covariates; and (3) estimate the standardized institution rates of prevalent dosing in excess of the typically described requirement for institution-level comparisons.

In response to reviewer requests in the context of the peer review process, we further conducted a hierarchical linear regression model in which the outcome of propofol dose was maintained as a continuous variable without reference to the FDA-approved package insert so as to understand factors associated with actual propofol induction dose across the range of prevalent dosing behaviors and in units of total milligrams to enhance clinical interpretability for practitioners.

In these multivariable models, we evaluated effect modification by age subgroups and ASA PS to investigate whether combinations of age and comorbidity affected providers' choice of propofol induction dose. Before regression models were constructed, the continuous explanatory variables under consideration for model inclusion were assessed for collinearity using the variance inflation factor with a threshold of 10 suggestive of substantial collinearity. All analyses were performed using the SAS statistical software, version 9.4 (Cary, NC). Within SAS, we fitted hierarchical models using the PROC GLIMMIX procedure. All statistical tests' p-values and confidence intervals were two-sided with a significance level for the primary outcome of 0.05.

2.4 | Institution-specific propofol dosing rates in excess of FDA's typical range

For institution effects, we compared predicted nonadherence rates (i.e., institution-specific or predicted) using both random institution effect and the fixed effect regression estimates to the fixed effects only (population-average or expected) rates. The intra-institution comparison of the two rates was used as a measure of institution performance in rates of incremental dosing in excess of the published typical range.[37,38]

2.5 | Discontinuous propofol dosing at 50 mg increments

We examined nonweight-adjusted anchoring effects in propofol dosing by measuring the tendency for induction doses to cluster at 50 mg increments (i.e., 50, 100, 150, 200, 250, and 300 mg). The percent of total doses occurring at each of these 50 mg increments was reported.

Sample size considerations: For the primary analysis estimating the prevalence of dosing in excess of the described typical dose range, a hypothetical subset of 10,000 cases with actual incremental dosing rates of 30% would produce a two-sided 95% CI of 29.1–30.9%. For such a hypothetical subset, power would exceed 99% to detect a hypothetical difference of 2% between observed dose range adherence and the 30% *a priori* benchmark, assuming an alpha of 0.05.

3 | RESULTS

Over 2.1 million patients aged ≥65 years underwent anesthetics during the observation period. After exclusions, a final sample of 350,766 patients from 36 institutions were included in the present analyses (see consort diagram Figure 1). The mean (SD) age was 73 (6.4), with 16.8% of the cohort aged over 80 years, 49.6% female, and 81.3% identified as white. Ethnic identification was poorly penetrant, with only 1.4% of the cohort identified as Hispanic. Characteristics of the included cohort are provided in Table 1. Due to nonrandom and significant missingness of preoperative laboratory data, only patients with complete data regarding hemoglobin and estimated GFR were included in multivariable models.

3.1 | Propofol induction dose by age and ASA PS

The percent of patients receiving propofol induction doses in excess of the typically described range was 64.8% (95% CI 64.6–65.0), with the mean (SD) weight-adjusted propofol dose being 1.7 (0.6) mg/kg. As shown in Figure 2, mean propofol dose exceeded the expected typical range across every age by ASA PS score classification except for patients with ASA PS 4. Within ASA PS 4, the proportion of patients that received propofol induction doses in excess of the typical range across the four age bins ranged from 43.1% in those aged 65–69 years to 26.9% in those aged 80 years or older. Propofol induction doses by age and ASA PS score are summarized in Figure 2 (see also histograms of weight-adjusted dose distributions displayed in Supplementary Figure S1 and summaries as listed in Supplementary Table S2).

3.2 | Independent predictors of propofol dose

In multivariable modeling, the prevalence of propofol induction dose in excess of the typically described range increased from 2014 through 2018. Such doses were more likely in males and patients identifying as Hispanic. In prior literature, it has been suggested that black versus white race may be implicated in differing clinical responses to propofol infusions,[39] but we observed no significant differences in prevalent dosing above the typical range associated with black versus white race. Increasing age and increasing obesity were negatively associated with exceeding the described range as was the use of adjunctive sedative medications. Doses exceeding the described range were less likely in sicker patients based on ASA PS, coronary artery disease, van Walraven Comorbidity Index, chronic kidney disease, and lower preoperative hemoglobin levels. While providers thus seemed to decrease induction dose for both older age and higher ASA PS score independently, the multiplicative interaction terms of these factors were not significant except for the interaction of age 80 and older with ASA

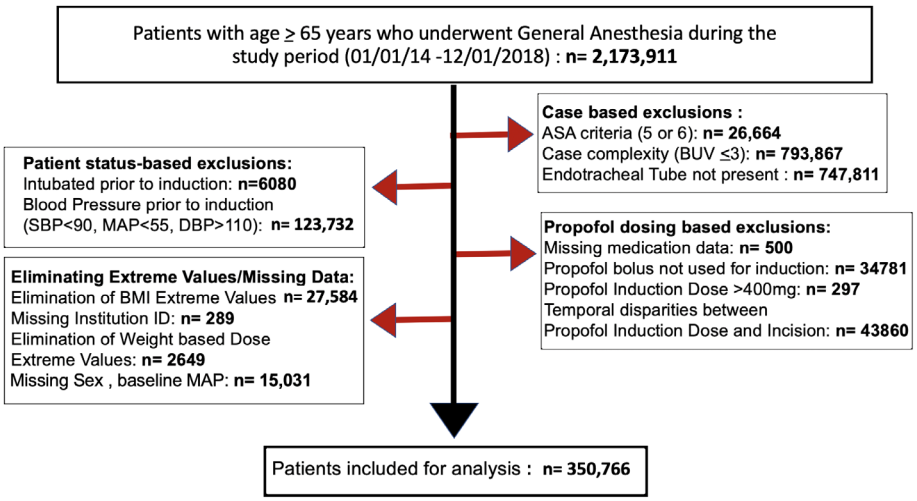


FIGURE 1 Consort diagram of inclusion and exclusion criteria [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Summary statistics of variables by propofol dose status

	Propofol dose above range (>1.5 mg/kg)		Total
	No (*N* = 123,492)	Yes (*N* = 227,274)	(*N* = 350,766)
Age in years			
65–69	034081 (27.60%)	096336 (42.39%)	130,417 (37.18%)
70–74	031762 (25.72%)	065298 (28.73%)	097060 (27.67%)
75–79	025821 (20.91%)	038742 (17.05%)	064563 (18.41%)
80 and older	031828 (25.77%)	026898 (11.84%)	058726 (16.74%)
Sex			
Female	057306 (46.40%)	116,533 (51.27%)	173,839 (49.56%)
Male	066186 (53.60%)	110,741 (48.73%)	176,927 (50.44%)
Race			
Black	008710 (07.05%)	015288 (06.73%)	023998 (06.84%)
Unknown/other race	014328 (11.60%)	027180 (11.96%)	041508 (11.83%)
White	100,454 (81.34%)	184,806 (81.31%)	285,260 (81.32%)
Ethnicity			
Hispanic ethnicity	001464 (01.19%)	003368 (01.48%)	004832 (01.38%)
Non-Hispanic ethnicity	113,766 (92.12%)	208,745 (91.85%)	322,511 (91.94%)
Unknown ethnicity	008262 (06.69%)	015161 (06.67%)	023423 (06.68%)
Year of surgery			
2014	016630 (13.47%)	027978 (12.31%)	044608 (12.72%)
2015	022328 (18.08%)	037942 (16.69%)	060270 (17.18%)
2016	024466 (19.81%)	043674 (19.22%)	068140 (19.43%)
2017	029356 (23.77%)	057333 (25.23%)	086689 (24.71%)
2018	030712 (24.87%)	060347 (26.55%)	091059 (25.96%)
Weight (kg)			
N (*N* missing)	123,492 (0)	227,274 (0)	350,766 (0)
Mean (SD)	85.67 (19.14)	78.41 (17.33)	80.97 (18.32)
Median (IQR)	83.9 (71.7–99.6)	77.1 (65.3–89.8)	79.4 (67.6–92.6)
Height (cm)			
N (*N* missing)	118,147 (5345)	218,237 (9037)	336,384 (14382)
Mean (SD)	169.47 (10.67)	168.22 (10.48)	168.66 (10.56)
Median (IQR)	170.2 (161.3–177.8)	167.6 (160.0–175.6)	167.9 (160.0–177.8)
WHO obesity class based on BMI			
Missing	005237 (04.24%)	008864 (03.90%)	014101 (04.02%)
Class I obesity (BMI 30 to <35)	029331 (24.80%)	041793 (19.14%)	071124 (21.13%)
Class II obesity (BMI 35 to <40)	014546 (12.30%)	014963 (06.85%)	029509 (08.77%)
Class III obesity (BMI ≥40)	007982 (06.75%)	005501 (02.52%)	013483 (04.00%)
Normal weight (BMI 18.5 to <25)	025694 (21.73%)	071786 (32.87%)	097480 (28.95%)
Overweight (BMI (25 to <30)	040181 (33.98%)	082611 (37.82%)	122,792 (36.47%)
Underweight (BMI <18.5)	000521 (00.44%)	001756 (00.80%)	002277 (00.68%)
ASA physical status			
Missing	2	3	5)
1	000379 (00.31%)	002042 (00.90%)	002421 (00.69%)

TABLE 1 (Continued)

	Propofol dose above range (>1.5 mg/kg)		Total
	No (*N* = 123,492)	Yes (*N* = 227,274)	(*N* = 350,766)
2	021745 (17.61%)	077474 (34.09%)	099219 (28.29%)
3	079122 (64.07%)	135,404 (59.58%)	214,526 (61.16%)
4	022244 (18.01%)	012351 (05.43%)	034595 (09.86%)
Emergency modifier			
Missing	000002 (00.00%)	000002 (00.00%)	000004 (00.00%)
Emergency	006978 (05.65%)	007456 (03.28%)	014434 (04.12%)
Nonemergency	116,512 (94.35%)	219,816 (96.72%)	336,328 (95.88%)
Neuraxial anesthetic			
No	122,233 (98.98%)	224,128 (98.62%)	346,361 (98.74%)
Yes	001259 (01.02%)	003146 (01.38%)	004405 (01.26%)
van Walraven Comorbidity Index			
N (*N* missing)	121,523 (1969)	224,680 (2594)	346,203 (4563)
Mean (SD)	7.94 (9.83)	5.85 (8.54)	6.59 (9.07)
Median (IQR)	5.0 (0.0–14.0)	3.0 (0.0–10.0)	4.0 (0.0–11.0)
Frailty index			
Missing	1969	2594	4563
High	1360 (1.12%)	1346 (0.60%)	2706 (0.78%)
Intermediate	12,863 (10.58%)	21,186 (9.43%)	34,049 (9.83%)
Low	107,300 (88.30%)	202,148 (89.97%)	309,448 (89.38%)
Coronary artery disease			
Missing	001969	002594	004563
No	086008 (70.78%)	188,756 (84.01%)	274,764 (79.36%)
Yes	035515 (29.22%)	035924 (15.99%)	071439 (20.64%)
Chronic kidney disease			
Missing	033033 (26.75%)	067618 (29.75%)	100,651 (28.69%)
Normal eGFR	011467 (12.68%)	028085 (17.59%)	039552 (15.81%)
Stage 2	046662 (51.58%)	093036 (58.27%)	139,698 (55.85%)
Stage 3a	018652 (20.62%)	025750 (16.13%)	044402 (17.75%)
Stage 3b	009991 (11.04%)	009968 (06.24%)	019959 (07.98%)
Stage 4	003687 (04.08%)	002817 (01.76%)	006504 (02.60%)
Anemia			
Missing	25,877	55,638	81,515
Mild	34,834 (35.69%)	52,325 (30.49%)	87,159 (32.37%)
Moderate to severe	16,739 (17.15%)	16,740 (9.75%)	33,479 (12.43%)
Normal	46,042 (47.17%)	102,571 (59.76%)	148,613 (55.19%)
Baseline mean arterial pressure			
Mean (SD)	97.42 (14.83)	99.71 (14.42)	98.91 (14.61)
Median (IQR)	97.0 (87.0–107.0)	99.0 (90.0–109.0)	99.0 (89.0–109.0)
Duration of surgery in minutes			
N (*N* missing)	123,230 (262)	226,980 (294)	350,210 (556)
Mean (SD)	216.24 (130.08)	206.89 (118.26)	210.18 (122.63)

(Continues)

TABLE 1 (Continued)

	Propofol dose above range (>1.5 mg/kg)		Total
	No (*N* = 123,492)	Yes (*N* = 227,274)	(*N* = 350,766)
Median (IQR)	188.0 (123.0–283.0)	180.0 (123.0–262.0)	183.0 (123.0–269.0)
Anesthesia base units			
Minor (≤5 base units)	029918 (24.23%)	056809 (25.00%)	086727 (24.73%)
Major (>5 base units)	093574 (75.77%)	170,465 (75.00%)	264,039 (75.27%)
Institution type			
Academic hospital	101,706 (82.36%)	192,473 (84.69%)	294,179 (83.87%)
Community hospital	021786 (17.64%)	034801 (15.31%)	056587 (16.13%)
Surgical service of proceduralist			
Cardiothoracic	011956 (09.68%)	007337 (03.23%)	019293 (05.50%)
General surgery	017561 (14.22%)	044462 (19.56%)	062023 (17.68%)
Medical—gastroenterology	007330 (05.94%)	006023 (02.65%)	013353 (03.81%)
Medical—other subspecialty	002821 (02.28%)	003938 (01.73%)	006759 (01.93%)
Neurosurgery	010454 (08.47%)	022486 (09.89%)	032940 (09.39%)
Gynecology	003474 (02.81%)	011793 (05.19%)	015267 (04.35%)
Ophthalmology	001585 (01.28%)	002423 (01.07%)	004008 (01.14%)
Oral/Maxillofacial/Otolaryngology	008120 (06.58%)	020702 (09.11%)	028822 (08.22%)
Orthopedics	019635 (15.90%)	034777 (15.30%)	054412 (15.51%)
Other	020230 (16.38%)	030573 (13.45%)	050803 (14.48%)
Plastic Surgery	001303 (01.06%)	004874 (02.14%)	006177 (01.76%)
Radiology	000883 (00.72%)	002216 (00.98%)	003099 (00.88%)
Thoracic	004462 (03.61%)	009535 (04.20%)	013997 (03.99%)
Transplant	000666 (00.54%)	001434 (00.63%)	002100 (00.60%)
Trauma	000901 (00.73%)	001200 (00.53%)	002101 (00.60%)
Urology	006153 (04.98%)	018193 (08.00%)	024346 (06.94%)
Vascular	005958 (04.82%)	005308 (02.34%)	011266 (03.21%)
Additional induction medications			
Etomidate			
Dose = 0 mg	119,347 (96.64%)	226,922 (99.85%)	346,269 (98.72%)
Dose >0 mg	4145 (3.36%)	352 (0.15%)	4497 (1.28%)
Ketamine			
Dose = 0 mg	115,981 (93.92%)	216,654 (95.33%)	332,635 (94.83%)
Dose >0 mg	7511 (6.08%)	10,620 (4.67%)	18,131 (5.17%)
Fentanyl (mcg)			
Mean (SD)	89.70 (69.97)	87.73 (59.96)	88.42 (63.67)
Median (IQR)	100.0 (50.0–100.0)	100.0 (50.0–100.0)	100.0 (50.0–100.0)
Midazolam (mg)			
Mean (SD)	0.68 (1.09)	0.64 (0.94)	0.66 (0.99)
Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)

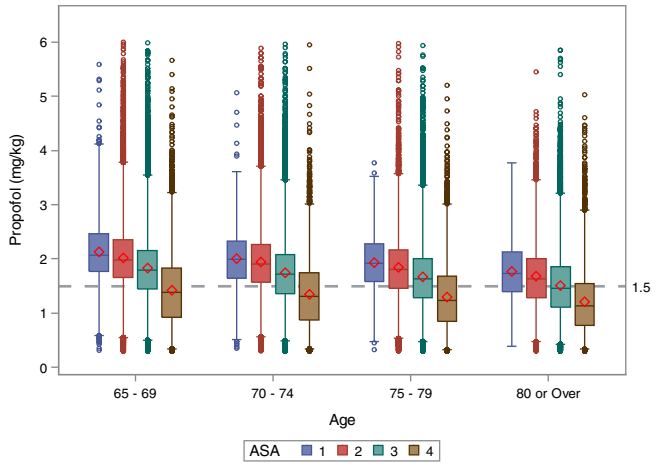


FIGURE 2 Boxplots of propofol dose by age and ASA PS. Diamonds show the mean, and shaded boxes show the 25–75% range with whiskers at 1.5 times the upper and lower bounds. The horizontal dotted line demonstrates the upper limit of the package insert's listed typical dosing requirement [Color figure can be viewed at wileyonlinelibrary.com]

PS score of 4. The full multivariable results are listed in Table 2 and Supplementary Table S3.

Regarding absolute propofol doses, factors associated with a mean decrease of at least 10 mg of propofol at induction included being aged over 75 years, ASA PS 4, and presenting for cardiothoracic, vascular, or gastrointestinal procedures.

Of note, while the propofol package insert suggests the slow administration of multiple doses of propofol over the course of a geriatric general anesthetic induction, the large majority (282,502 or 81%) of the 350,766 included cases in our cohort showed recorded induction doses charted as a single bolus dose, a finding that should be interpreted cautiously since closely timed doses may be recorded as one administration. Patients charted as receiving a single bolus dose versus multiple doses were similar in respect to age (mean 72.9 vs. 73.3 years; median age of both groups = 72 years).

3.3 | Institution-specific rates of dosing in excess of FDA's typical range

In unadjusted analysis, significant variations in care patterns were demonstrated, with incremental dose rates ranging from 38% to 82% across centers, a difference that cannot be explained solely by differences in the distributions of ASA PS scores or of age (see Figure 3). After adjusting for case-mix and patient characteristics, we observed four institutions with random effects predicted incremental dose rates that differed by more than 1% of their fixed effects or population averaged estimates. For these outlying institutions, the actual versus expected rate of incremental dose rates in excess of FDA's typical range varied from a high of 106% to a low of 92% of predicted.

3.4 | Propofol dose discontinuity at 50 mg increments

Total induction doses of propofol demonstrated anchoring at 50 mg increments in 60.9% of cases, with more than 1 in 5 doses equaling 150 mg. A histogram of all propofol doses by 10 mg increments is included, demonstrating multimodal anchoring across the breadth of the distribution (see Supplementary Figure S4).

4 | DISCUSSION

This is the first multicenter study to examine propofol dosing practices in relation to the medication label's typical dose range for older patients undergoing surgical procedures in the United States, and the present analysis confirms our primary hypothesis that there is widespread discordance between current geriatric anesthetic practice in the United States and the package label's description of the typical dose range. Observed doses exceeded the typical dose range by a mean of 13% overall, and significant numbers of patients received higher than expected induction doses regardless of age and comorbidity. Remarkably, over one quarter of the sickest and oldest patients in our sample (i.e., ASA PS 4 patients aged ≥80 years) received propofol exposures at induction that would be considered above the typical expected dose requirement for a cohort of healthy patients 25 years younger. Although it remains unknown what threshold of propofol induction dosing outside of typical ranges may lead to untoward downstream effects, the discordance between what the package-insert states to be "typical" and the prevalent anesthetic induction dosing practice that we have documented raises the question as to whether the FDA-approved label or the prevalent practice pattern is in need of revision.

Regarding institution-specific behaviors, while we saw variation across institutions in unadjusted proportions of patients receiving incremental doses beyond the typical range, those differences were less apparent in adjusted analyses that accounted for differences in patient mix and procedure type. Still, institutional differences of greater than 1% observed over expected incremental dosing do persist in some centers and seem to be robust within the limits of our adjusted modeling. These results should be interpreted cautiously as they were not

TABLE 2 Multivariable analysis evaluating perioperative factors associated with odds of propofol dose above range ($N = 228,492$ with preoperative laboratory data)

Variable	Odds ratio (95% CI)	p-Value
Age, years		<0.0001*
65–69	Ref	
70–74	0.603 (0.388 to 0.939)	0.0253
75–79	0.419 (0.229 to 0.766)	0.0047
80 and older	0.128 (0.065 to 0.253)	<0.0001
Sex (female vs. male)	0.744 (0.722 to 0.767)	<0.0001
Race		<0.0001*
Black	1.036 (0.996 to 1.077)	0.0788
Unknown/other	0.772 (0.736 to 0.81)	<0.0001
White	Ref	
Ethnicity		<0.0001*
Hispanic	1.204 (1.106 to 1.31)	<0.0001
Unknown	1.277 (1.192 to 1.367)	<0.0001
Non-Hispanic	Ref	
Year of surgery		<0.0001*
2014	Ref	
2015	1.029 (0.992 to 1.068)	0.1266
2016	1.029 (0.992 to 1.067)	0.1257
2017	1.166 (1.125 to 1.208)	<0.0001
2018	1.186 (1.145 to 1.228)	<0.0001
Weight, kg	0.969 (0.967 to 0.971)	<0.0001
Height (cm)[a]	1.000 (0.997 to 1.002)	0.8078
WHO obesity class		<0.0001*
Normal weight (BMI 18.5 to <25)	Ref	
Overweight (BMI (25 to <30)	0.916 (0.882 to 0.951)	<0.0001
Class I obesity (BMI 30 to <35)	0.831 (0.78 to 0.886)	<0.0001
Class II obesity (BMI 35 to <40)	0.806 (0.734 to 0.884)	<0.0001
Class III obesity (BMI ≥40)	0.739 (0.651 to 0.839)	<0.0001
Underweight (BMI <18.5)	1.029 (0.902 to 1.174)	0.6713
ASA physical status		<0.0001*
1	Ref	
2	0.793 (0.607 to 1.035)	0.0873
3	0.539 (0.414 to 0.703)	<0.0001
4	0.225 (0.172 to 0.294)	<0.0001
Age × ASA physical status interaction		<0.0001*
70–74 × 2	1.075 (0.688 to 1.679)	0.7504
70–74 × 3	1.104 (0.708 to 1.72)	0.6624
70–74 × 4	1.268 (0.809 to 1.987)	0.3006
70–74 × 1	Ref	
75–79 × 2	0.955 (0.52 to 1.751)	0.8804
75–79 × 3	1.072 (0.586 to 1.962)	0.8208
75–79 × 4	1.366 (0.743 to 2.511)	0.3154

TABLE 2 (Continued)

Variable	Odds ratio (95% CI)	p-Value
75–79 × 1	Ref	
80 and older × 2	1.391 (0.705 to 2.744)	0.3419
80 and older × 3	1.64 (0.833 to 3.229)	0.1523
80 and older × 4	2.463 (1.246 to 4.867)	0.0095
80 and older × 1	Ref	
Emergency modifier	0.697 (0.667 to 0.729)	<0.0001
Neuraxial anesthesia, yes	1.371 (1.26 to 1.491)	<0.0001
van Walraven comorbidity index	0.991 (0.99 to 0.992)	<0.0001
Frailty index		<0.0001*
High	0.828 (0.749 to 0.915)	0.0002
Intermediate	1.04 (1.007 to 1.074)	0.017
Low	Ref	
Coronary artery disease	0.76 (0.741 to 0.778)	<0.0001
Chronic kidney disease		<0.0001*
Stage 2	1.033 (1.003 to 1.065)	0.0302
Stage 3a	0.957 (0.924 to 0.991)	0.0143
Stage 3b	0.879 (0.841 to 0.918)	<0.0001
Stage 4	0.804 (0.753 to 0.858)	<0.0001
Normal eGFR	Ref	
Anemia		<0.0001*
Mild	0.831 (0.812 to 0.849)	<0.0001
Moderate to severe	0.642 (0.621 to 0.663)	<0.0001
Normal	Ref	
Baseline mean arterial pressure	1.012 (1.011 to 1.013)	<0.0001
Duration of surgery in minutes[b]	0.997 (0.997 to 0.998)	<0.0001
Anesthesia base units > 5	1.1 (1.069 to 1.131)	<0.0001
Academic vs. community hospital	1.064 (1.033 to 1.095)	<0.0001
Surgical service of proceduralist		<0.0001*
General surgery	Ref	
Cardiothoracic	0.344 (0.328 to 0.36)	<0.0001
Medical—gastroenterology	0.437 (0.411 to 0.463)	<0.0001
Medical subspecialty	0.606 (0.563 to 0.652)	<0.0001
Neurosurgery	0.803 (0.773 to 0.833)	<0.0001
Gynecology	1.078 (1.02 to 1.138)	0.0072
Ophthalmology	0.525 (0.449 to 0.614)	<0.0001
Oral/Maxillofacial, ENT	0.82 (0.782 to 0.859)	<0.0001
Orthopedics	0.703 (0.68 to 0.726)	<0.0001
Other	0.63 (0.606 to 0.655)	<0.0001
Plastic surgery	1.138 (1.029 to 1.26)	0.0122
Radiology	1.16 (1.052 to 1.279)	0.0029
Thoracic	0.755 (0.719 to 0.793)	<0.0001
Transplant	0.629 (0.535 to 0.739)	<0.0001
Trauma	0.592 (0.531 to 0.66)	<0.0001

(Continues)

TABLE 2 (Continued)

Variable	Odds ratio (95% CI)	p-Value
Urology	1.071 (1.024 to 1.12)	0.0028
Vascular	0.462 (0.438 to 0.488)	<0.0001
Etomidate (yes vs. no)	0.067 (0.059 to 0.077)	<0.0001
Ketamine (yes vs. no)	0.573 (0.55 to 0.598)	<0.0001
Midazolam (mg)	0.886 (0.876 to 0.895)	<0.0001
Fentanyl (mcg)[c]	0.99 (0.986 to 0.994)	<0.0001

Note: Individual Institution was treated as a random effect to account for possible similarity among patients cared at each institute. A total of 228,492 patients were included in the above analysis.

*Type III test *p*-value.

[a]Per 10 cm increase.

[b]Per 10 min increase.

[c]Per 25 mcg increase.

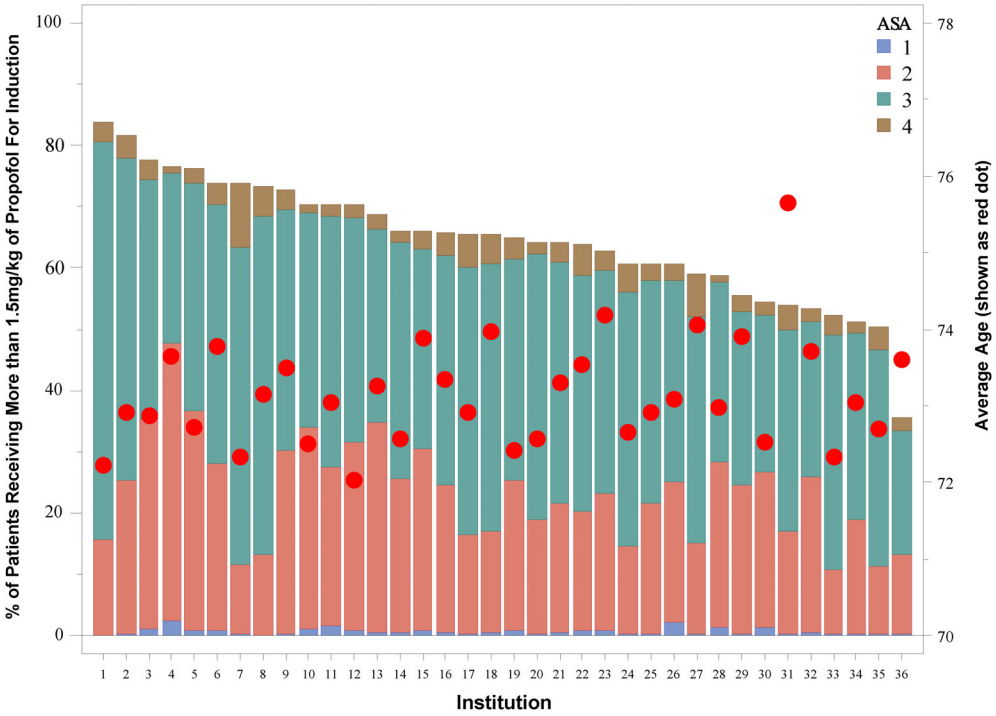


FIGURE 3 Percent of patients receiving propofol incremental induction dose above 1.5 mg/kg by institution is shown on the *y* axis at left. Shading shows distribution of ASA PS by Institution. Red dots demonstrate mean age by institution on the *y* axis at right

the primary inferential hypothesis of the study and should be understood as hypothesis generating rather than definitive evidence of care disparities across institutions.

Regarding dose anchoring, our descriptive analysis demonstrates significant discontinuities in the choice of administered induction dose at intervals of 50 mg. More than half of all patients received 100 mg, 150 mg, or 200 mg of propofol. We conjecture that such anchoring is likely to exacerbate connections between patient weight and rate of dosing in excess of the typical range. For example, a 150 mg induction dose discontinuously becomes an incremental dose above typical range for patients weighing less than 100 kg but remains concordant within the FDA-described range for heavier patients. It may thus prove important to account for this multimodal, irregular distribution in the design of future outcomes studies that seek to elucidate effects of propofol dosing patterns on important patient outcomes.

4.1 | Limitations

Several limitations of the present analysis should be noted. First, our conclusions are based on documented medication dosing that may contain inaccuracies in relation to actual practice. In our cohort, a minority (19%) of cases were noted to have more than one bolus induction

dose of propofol, but some induction doses that were slowly titrated may have been added together during the process of clinical documentation. Although it is certainly the case that some providers engage in careful titration of induction doses, based on our present data and our own clinical experience, such titration is far from routine. Although similar observational studies are subject to recording accuracy, MPOG data collection standards include a robust multicenter validation schema, incorporating case-by-case monthly validations at each participating center, and these data have been used in a variety of high-quality observational studies.[21,40]

Another possible limitation of our analysis may stem from our selection of four coarsened categories for age in our assessments of incremental dosing prevalence. Although it is possible there could be a loss of information by grouping ages into subcategories, categorizing age should allow for detecting trends, can be useful for identifying thresholds across age, and allows one to model nonlinearities between age and incremental dose. Although we were cognizant of the hazards of binning ages into subcategories, we chose this method of displaying data so as to improve interpretability of the data as they relate to age and comorbid status and thereby to promote a better understanding of the interactions among these two factors.

It is also important to note that the typical dose range, as described on the package label, does not include a description of the shape of the typical dose range curve. Nevertheless, regardless of the distribution's shape, it remains inconsistent with what our analysis shows to be the prevalent induction dosing used in clinical practice. Well less than 50% of geriatric patients are receiving an induction dose in the listed "typical" range, and this observation demonstrates a remarkable discordance that remains to be understood in future work.

Another issue to be highlighted is that while we included non-propofol sedatives in our modeling, it is not clear how to interpret their concomitant dosing in relation to an expected propofol dose range. Patients receiving concomitant sedative medications were less likely to receive propofol doses above the listed typically expected range, suggesting that practitioners anticipate desired clinical endpoints to drive dose adjustment.

Finally, the clinical relevance of our observation regarding induction dosing for patient-centered outcomes remains unclear. It would be overly simplistic to extrapolate that older patients are being "overdosed." Future studies of appropriately matched patients with outcomes data are required to understand the potential for and extent of any differences in relevant clinical course that may be attributable to the propofol induction dosage patterns described here. The effort to define clinical phenotypes that may define varying degrees of patient resilience to anesthetic induction dosing practices remains an area of great importance, with opportunities for future collaboration among geriatricians and anesthesiologists.

In conclusion, the present study provides the broadest and most thorough documentation to date of the widespread use of propofol in excess of the published typical dose range during the conduct of modern general anesthetic induction of elderly surgical patients. The potential significance of this discordance on patient outcomes—both in general and within particularly vulnerable subsets of the elderly—deserves dedicated study. At present, it remains unclear whether a change in drug labels or a change in prevalent anesthetic induction dosing practice may be warranted.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors have reviewed and approve of the final manuscript submission. Robert B. Schonberger: concept and design, data analysis, interpretation of data, and preparation of manuscript. Amit Bardia: concept and design, data analysis, interpretation of data, and preparation of manuscript. Feng Dai: concept and design, data analysis, interpretation of data, and preparation of manuscript. George Michel: data analysis and interpretation of data. David Yanez: concept and design, data, analysis, interpretation of data, and preparation of manuscript. Jeptha Curtis: concept and design, interpretation of data, and preparation of manuscript. Michelle T. Vaughn: concept and design, data analysis, and interpretation of data. Matthew M. Burg: concept and design, data analysis, interpretation of data, and preparation of manuscript. Michael Mathis: concept and design, interpretation of data, and preparation of manuscript. Sachin Kheterpal: concept and design, interpretation of data, and preparation of manuscript. Shamsuddin Akhtar: concept and design, data analysis, interpretation of data, and preparation of manuscript. Nirav Shah: concept and design, data analysis, interpretation of data, and preparation of manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Supplementary Figure S1: Histograms of propofol induction dose by age bin and ASA physical status. Vertical dotted line demonstrates the upper limit of the listed typical dosing range.

Supplementary Table S2: Absolute and weight-adjusted propofol induction dose by age and ASA physical status.

Supplementary Table S3: Multivariable analysis evaluating perioperative factors associated with variability in absolute propofol dose received at induction.

Supplementary Figure S4: Histogram of absolute propofol dose in milligrams for the entire data set.

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