

Effect of Patient Characteristics and Pre-Procedure Midazolam on Propofol Dosing for Esophagogastroduodenoscopy in Children

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Abstract

Background: Propofol use is common for children undergoing esophagogastroduodenoscopy (EGD). Appropriate dosing is crucial to facilitate endoscope insertion and avoid respiratory compromise from under or over sedation.

Aim: Examine propofol dosing and the effects of weight, body mass index (BMI), and pre-procedural midazolam on propofol dosing in children undergoing EGD.

Methods: Data were collected in a prospective study on patients (ages 1-17 years) who underwent EGD with propofol sedation at a single center. Patient age, weight, and pre-procedural midazolam dose were recorded. Propofol induction and total dose, and any adverse respiratory events were recorded. Induction dose was defined as that given to complete successful endoscope insertion and complete 30 seconds of the procedure. Total dose was induction dose plus additional dose to complete the procedure. Three patient sub-groups were defined by weight (<20 Kg, 20-49.99 Kg, and ≥50 Kg). Induction and total propofol dosing differences were compared between weight groups as was the effect of pre-procedural midazolam.

Results: Complete data were available for 675 subjects (mean ± SD age 11.2 ± 4.5 years). Significantly greater induction doses of propofol (mg/kg) were required for induction with decreasing weight categories: 6.2 ± 1.8 mg/kg vs. 4.9 ± 1.3 mg/kg vs. 3.5 ± 1.0 mg/kg, for <20 Kg, 20-49.99 Kg, and ≥50 Kg respectively; p<0.001. Total time of EGD (minutes) was significantly less in the lower weight groups (4.3 ± 1.3 min vs. 4.8 ± 1.3 min vs. 4.9 ± 1.2 min, respectively; p<0.001). Overweight (BMI>85%)/obese (BMI>95%) children required less induction and total dose (mg/kg) (p<0.001). Lower induction doses were required for children who received midazolam premedication compared to children who received no premedication in both <20 Kg (5.8 ± 1.6 mg/kg vs. 6.5 ± 1.9 mg/kg, p<0.03) and 20-49.99 Kg (4.4 ± 1.1 mg/kg vs. 4.9 ± 1.4 mg/kg, p<0.02) groups.

Conclusions: Lower weight children require higher induction propofol doses (mg/kg) to achieve adequate sedation. Premedication with midazolam decreased induction propofol requirements. These data will serve as a useful guide for clinicians.

Keywords: Propofol; Esophagogastroduodenoscopy; Midazolam; Children; Adolescents

Introduction

Esophagogastroduodenoscopy (EGD) is commonly performed by pediatric gastroenterologists and surgeons for the diagnosis and management of children with various gastrointestinal disorders. Appropriate sedation is required to ensure patient comfort and safety while completing the procedure in a timely manner. The choice of sedation varies widely and is often institution dependent and can include general anesthesia with endotracheal intubation, propofol given by bolus or continuous infusion, or a combination of benzodiazepines and opioids (e.g., midazolam/fentanyl). In our institution, propofol, alone or in combination with preoperative benzodiazepine, has become the methodology of choice to perform EGD. Its rapid onset of action, ease of titration and short duration of action make it ideally suited for pediatric EGD, allowing for early patient recovery and discharge [1-3].

Appropriate initial propofol dosing is crucial in achieving a deep enough level of sedation to permit safe and effective insertion of the endoscope. Insufficient depth of anesthesia can result in inability to pass the endoscope, difficulty in completing the procedure, as well as increased morbidity related to airway complications such as laryngospasm, bronchospasm, coughing, retching, vomiting and aspiration. Overdosing propofol can result in apnea, oxygen desaturation and hypotension. Our clinical observations have suggested that younger children often require deeper sedation as well as an increased weight based dosing of propofol (mg/kg) compared to older children or adults in order to perform EGD without complication. Appropriate dosing is left to the discretion of the anesthesia provider to balance unhindered insertion of the scope with preservation of airway patency and respiratory stability. While dosing guidelines for procedural sedation exist [4,5], there are limited retrospective pediatric data specific to propofol dosing specifically for EGD to avoid unwanted adverse events [6].

In this prospective study we aimed to systematically gather data to better understand the effect of patient characteristics (weight, age, gender, body mass index (BMI)) as well as pre-procedural midazolam on propofol dosing in children and adolescents undergoing EGD. These data could serve as a useful reference for anesthesia providers less familiar with sedation for pediatric EGD and permit safer and more effective propofol dosing.

Methods

Study population

Ambulatory children at Connecticut Children's Medical Center from age 1 through 17 years and ASA Classification I or II undergoing diagnostic EGD as a single procedure utilizing propofol for anesthesia were eligible for study. Children were excluded if there were a congenital or other condition that would affect anesthesia requirements, behavioral issues that impaired initial sedation, seizure disorder requiring anticonvulsants, tracheostomy, current respiratory infection or reactive airway disease, ASA classification III or greater, or general anesthesia accomplished by mask induction followed by propofol maintenance (used when difficult IV access is encountered). Only cases in which a board certified pediatric gastroenterologist (n=6) was performing the entire procedure and a board certified pediatric anesthesiologist (n=10) was administering sedation were considered. No trainee pediatric gastroenterologist or trainee anesthesiologist-associated procedures were studied. Standard American Society for Anesthesiology (ASA)

monitoring including cardiac, oxygen saturation, and CO₂ assessment are provided to all patients during EGD, and all patients receive nasal cannula oxygen prior to and during the procedure. Approximately 1200 EGDs are performed annually under propofol at our institution.

We defined 3 patient sub-groups by weight: <20 kg, 20-49.9 kg, and ≥ 50 kg, largely corresponding to pre-school children, school age children, and adolescents, respectively. Patient data recorded at the time of the procedure included age, gender, weight, height, body mass index (BMI), and pre-procedural sedation with oral midazolam if given. Overweight was defined as a BMI at or above the 85th percentile and lower than the 95th percentile for children of the same age and sex as seen on the CDC Growth Charts. Obesity was defined as a BMI at or above the 95th percentile for children of the same age and sex as seen on the CDC Growth Charts.

Propofol dosing

Propofol dosing was left to the discretion of the anesthesiologist and given by bolus push rather than continuous infusion throughout the procedure. An induction and total propofol dose were recorded. The induction dose of propofol was defined as the total amount given by the anesthesiologist to allow successful insertion of the endoscope to begin the procedure and continue for at least 30 seconds without the need for endoscope removal. If within 30 seconds of endoscope insertion additional propofol was required for sedation, that amount was added to determine the total induction dose. In order to ensure standardization between endoscopists and anesthesia providers, the anesthesia provider ensured by direct query that the endoscopist was ready to start the procedure immediately following administration of the induction dose. A single endoscopy nurse was responsible for documenting when 30 seconds had expired following the insertion of the endoscope and recorded the amount of propofol given to that point. The timing interval started upon the first attempt to orally insert the endoscope. The endoscopy nurse recorded the total dose of propofol used for the case as well as the total time from initial insertion of the endoscope to final withdrawal. Standard diagnostic EGD includes 3-6 grasp biopsies from the duodenum, stomach, and esophagus, respectively. If intravenous lidocaine or fentanyl were given prior to propofol the dose was recorded.

Adverse events

Adverse events recorded during the procedure included: oxygen

desaturations to <85% lasting for ≥10 seconds, laryngospasm, bronchospasm, need for an oral or nasal airway, bag-valve-mask assisted ventilation, or intubation.

Statistical Analysis

Based on our uncontrolled observations we estimated that there would be a 20% difference in propofol requirements between < 20 kg vs. 20-49.9 kg groups, and a 20% difference between 20-49.9 kg vs ≥50 kg groups. Sample size calculation was performed for several scenarios, varying the percent difference in dose between age groups from 15% to 30%, the range of doses commonly used in older pediatric patients from 2-3 mg/kg, and the number of groups being compared (2 or 3). For a one-way analysis of variance, samples of 85 per group are adequate to detect small to medium differences in propofol dosing between the age groups (standardized effect sizes of .2 and larger) for significance level .05 and power .80. We proposed to study at least 120 subjects in each of the 3 groups to allow evaluation of the effects of age, BMI, and oral midazolam use on propofol dosing. Induction and total procedure dosing differences were compared between groups using analysis of variance followed by appropriate multiple comparisons tests. Effects due to BMI, oral midazolam, and other potential confounders were also explored using analysis of variance and multiple linear and logistic regression. Data are expressed as mean ± SD.

This study was approved by the Institutional Review Board of Connecticut Children’s Medical Center.

Results

Complete data were available for 675 diagnostic EGD studies. Demographic and clinical characteristics of the 3 study groups are shown in Table 1 with 120 subjects <20kg, 309 from 20-49.9 kg, and 246 ≥ 50 kg. Fifty-one percent of all patients were male. Differences noted in BMI between the 3 study groups were expected with a higher proportion of underweight children in the youngest group and increasing frequency of overweight and obesity in the older children. Pre-procedure midazolam was given in 48% of the <20 kg group compared to 12% in the middle weight group and only 3% of the heaviest group. Lidocaine prior to propofol was given in 85% of all patients. Fentanyl was used in 6% of all procedures, ranging from 3% of the lightest group to 8% of the heaviest group.

Propofol dosing by weight

Table 1: Clinical and demographic characteristics of study population.

	All Patients (N=675)	Weight (kg) at Endoscopy		
		< 20 kg (N=120)	20-49.9 kg (N=309)	≥ 50 kg (N=246)
Age at Endoscopy	11.2 ± 4.5	4.3 ± 2.1	10.6 ± 2.9	15.2 ± 2.0
Gender (Male)	339 (51%)	70 (59%)	155 (51%)	114 (47%)
Height (cm)	141.5 ± 25.9	99.0 ± 12.0	139.3 ± 14.2	164.7 ± 9.9
Weight (kg)	42.4 ± 22.1	15.1 ± 3.2	34.1 ± 8.8	66.1 ± 15.1
Body Mass Index (BMI)***	19.5 ± 5.2	15.3 ± 1.7	17.3 ± 2.5	24.4 ± 5.2
Weight Class by BMI****				
Underweight	52 (8%)	22 (21%)	26 (9%)	4 (2%)
Normal weight	446 (68%)	79 (74%)	231 (76%)	136 (56%)
Overweight	71 (11%)	3 (3%)	28 (9%)	40 (17%)
Obese	85 (13%)	3 (3%)	19 (6%)	63 (26%)
Midazolam pre-medication***	102 (15%)	58 (48%)	37 (12%)	7 (3%)
Concomitant IV fentanyl pre-procedure	40 (6%)	3 (3%)	17 (6%)	20 (8%)
Lidocaine IV pre-procedure	575(85%)	102 (85%)	260 (84%)	213 (87%)

Data expressed as mean ± standard deviation or frequency (%).

Missing data excluded from table.

^Underweight= <5th percentile, Normal= 5th-84.9th percentile, Overweight= 85th-94.9th percentile, Obese= ≥95th percentile.

*** p<.001 comparing the three weight groups.

Induction and total propofol dosing as well as EGD duration as a function of patient weight are shown in Table 2. Significantly different mg/kg dosing was required for both induction and total dosing between the 3 weight groups with the lower weight children requiring the greatest dose (p<.001). The difference in the mean total dose between the lightest and heaviest groups was approximately 3 mg/kg. The differences between the 3 groups in total propofol was largely based on differences in induction dosing as the post-induction dosing (total dose minus induction dose) was 1.8 mg/kg, 1.8 mg/kg, and 1.5 mg/kg in the 3 groups, respectively.

Of note, though the <20 kg group required the largest total mg/kg dosing of propofol, the mean duration of the EGD was shortest in this group. Indeed, while significant differences in mean EGD duration were noted between the groups, the longer duration groups had a smaller propofol requirement. The effect of weight on propofol dosing is seen in Table 3. Among children weighing ≥50 kg, those with BMIs classified as overweight or obese required significantly less propofol (mg/kg) for induction and total mg/kg dosing than normal weight children (p<.001). Dosing differences between normal and overweight/obese patients weighing 20-49.9 kg were not statistically significant.

To evaluate individual effects of both weight and BMI weight class, multiple regression analysis was performed using induction and total dose as outcomes and gender, weight, and BMI weight class as potential predictors. Weight and BMI class were independently associated with both induction and total dose (at levels <.005 for a variety of models) in the direction reported above. Gender differences were not statistically significant.

Pre-procedural midazolam

The effect of pre-procedural midazolam on propofol requirement was examined in the <20 kg and 20-49.9 kg patient groups only since very few patients (7/246) weighing ≥50 kg received midazolam. Pre-procedural midazolam dosing was 0.29 ± 0.04 mg/kg in the <20 kg group and 0.31 ± 0.06 mg/kg in the 20-49.9 kg group. When comparing induction and total propofol dosing in the <20kg subjects, those who

received pre-procedural midazolom received 5.8 ± 1.6 mg/kg induction and 7.6 ± 2.4 mg/kg total (n=58) compared to 6.5 ± 1.9 mg/kg induction and 8.4 ± 2.2 mg/kg total (n=62) in those who did not receive midazolom (p<.03 for induction dose comparison). Among subjects 20-49.9 kg, those who received pre-procedure midazolom received 4.4 ± 1.1 mg/kg induction and 6.0 ± 1.9 mg/kg total (n=37) compared to 4.9 ± 1.4 mg/kg induction and 6.8 ± 1.7 mg/kg total (n=272) for those who did not receive pre-procedure midazolom (p<.02 for induction and p<.01 for total dose). The differences in total dose between those receiving and not receiving midazolom was driven by the induction doses as the post-induction doses were similar between those receiving and not receiving midazolom.

Adverse events

No patient required intubation, while 19 patients (3%) required bag-mask ventilation for oxygen desaturation. Bag mask ventilation was more commonly required for the children in the <20 kg group (8% vs. 2% vs. 2% for the three respective weight groups), p<.01). Bronchospasm, laryngospasm, or use of oral or nasal airway were each observed in <0.5% of patients. The most common adverse event was oxygen desaturation to <85% which was noted in 49% of the <20kg group, 24% of the middle weight group and 17% of the heaviest group (p<.001).

We next examined the potential relationship of propofol dosing and pre-procedural midazolam to the occurrence of oxygen desaturation to <85% as well as the need for bag mask ventilation. In the <20 kg group a total of 59 patients had oxygen desaturation compared to 61 who did not. Mean propofol doses were 6.7 ± 1.3 mg/kg induction and 8.4 ± 2.0 mg/kg total in the former group compared to 5.7 ± 2.0 mg/kg induction and 7.7 ± 2.6 mg/kg total in the latter group (p<.001). For those 59 patients who had oxygen desaturation, 54% received pre-procedure midazolom compared to 43% of the 61 patients who did not experience desaturation. There was no difference noted in midazolom doses in mg/kg between those <20 kg subjects who did and did not experience desaturation (0.29 ± 0.05 vs. 0.29 ± 0.02).

Table 2: Induction and Total Propofol Dose (mg/kg) for EGD by Patient Weight.

	All Patients (N=675)	Weight at Endoscopy		
		< 20 kg (N=120)	20-49.9 kg (N=309)	≥ 50 kg (N=246)
Propofol Dose (mg/kg)				
Induction***	4.6 ± 1.6	6.2 ± 1.8	4.9 ± 1.3	3.5 ± 1.0
Total Endoscopy***	6.3 ± 2.1	8.0 ± 2.4	6.7 ± 1.7	5.0 ± 1.4
EGD duration (minutes)***	4.7 ± 1.2	4.3 ± 1.3	4.8 ± 1.3	4.9 ± 1.2

Data expressed as mean ± standard deviation.

Missing data excluded from table.

*** p<.001 comparing the three weight groups.

Table 3: Induction and Total Propofol Dose (mg/kg) by Patient Weight and Weight Class by Body Mass Index (BMI) Percentile.

WEIGHT GROUP	WEIGHT CLASS BY BMI PERCENTILE [^]		
	UNDERWEIGHT	NORMAL WEIGHT	OVERWEIGHT/OBESE
INDUCTION DOSE (mg/kg)			
< 20 kg	7.0 ± 2.4 (22)	6.0 ± 1.6 (79)	5.6 ± 1.0 (6)
20-49.9 kg	5.4 ± 1.2 (26)	4.8 ± 1.4 (231)	4.7 ± 1.3 (47)
≥ 50 kg	3.4 ± 0.4 (4)	3.8 ± 1.1 (136)***	3.2 ± 0.8 (103)***
TOTAL DOSE (mg/kg)			
< 20 kg	9.0 ± 2.7 (22)	7.8 ± 2.2 (79)	7.7 ± 2.9 (6)
20-49.9 kg	7.5 ± 2.2 (26)	6.7 ± 1.6 (231)	6.2 ± 1.9 (47)
≥ 50 kg	5.2 ± 0.6 (4)	5.2 ± 1.5 (136)***	4.6 ± 1.2 (103)***

Data expressed as mean ± standard deviation (number of patients).Missing data excluded from table.

[^]Underweight= <5th percentile, Normal= 5th-84.9th percentile, Overweight/Obese= ≥85th percentile.

*** p<.001 comparing patients with normal weight to patients who are overweight/obese.

In the 20-49.9 kg group a total of 74 patients had oxygen desaturation compared to 234 who did not. Mean propofol doses were not significantly different in the former compared to the latter group, 5.1 ± 1.4 mg/kg induction and 6.7 ± 2.0 mg/kg total versus 4.8 ± 1.3 mg/kg induction and 6.7 ± 1.7 mg/kg total. For those 74 patients who had oxygen desaturation 19% received pre-procedural midazolam compared to 10% of the 234 patients who did not experience desaturation ($p < .05$). There was no difference noted in midazolam doses in mg/kg between those 20-49.9 kg subjects who did and did not experience desaturation (0.33 ± 0.06 vs. 0.30 ± 0.06 , respectively). Among all patients < 50 kg, the odds ratio (95% confidence interval) for desaturation among patients who received midazolam compared to those who did not receive midazolam is 3.13 (2.03-4.85, $p < .001$).

Discussion

Though propofol requirements for successful EGD are highly variable, it is generally well-established that there is a linear decrease in propofol dosing with increasing age⁷. The ED₅₀, or dose of propofol required for loss of the eyelash reflex, increases with decreasing age (i.e., smaller children require a larger dose per kg of body weight). There are well established doses of propofol to be given in order to blunt the hemodynamic effects of intubation after sevoflurane induction in children for tonsillectomy and adenoidectomy⁸. To our knowledge, there are no large prospective studies examining the range of propofol dosing that is appropriate for children undergoing EGD. Our study sought to offer dosing guidelines for pediatric anesthesiologists not familiar with dosing propofol for successful and uncomplicated completion of EGD in pediatric patients

Our study demonstrates that induction propofol dosing in lower weight children was significantly higher on a mg/kg basis than children with a higher weight undergoing EGD. Propofol is highly lipophilic and therefore rapidly distributes to vessel rich organs which accounts for its rapid onset. A child's large central compartment will require twice the induction dose of an adult [9]. Children have a larger volume of distribution and, therefore, rapid redistribution will require multiple doses or a continuous infusion to maintain an adequate depth of anesthesia compared to adults [9]. Clearance is also greater than that of adults, again resulting in the need for repeated dosing or continuous infusion [9].

Children with higher BMI, considered obese or overweight, required less propofol (mg/kg) than their normal weight counterparts. In the obese population, fat increases to a greater extent than lean body weight and cardiac output preferentially goes to lean tissue over adipose tissue [10]. It has been shown that dosing propofol by lean body weight as opposed to total body weight in morbidly obese subjects may be more appropriate [10]. In that study, the dose of propofol to achieve loss of consciousness was similar between their control subjects (propofol dosing based on total body weight) and their morbidly obese subjects based on lean body weight suggesting that lean body weight should be the dosing scale for morbidly obese patients.

At our institution, pre-procedural oral midazolam is often given to younger children to facilitate IV placement. Our study showed a reduction in the amount of induction propofol given in the children who had received oral midazolam as a premedication. While the advantages of propofol for EGD are its rapid onset, ease of titration, and short half-life, the unwanted side effects of propofol include respiratory depression, obstructive apnea, oxygen desaturation and hypotension. In theory, adding a benzodiazepine would reduce the amount of propofol needed on induction and in turn decrease the rate of unwanted side effects mentioned above. This is indeed what we found. Another potential issue with the additional use of midazolam might be a longer time in recovery following the endoscopic procedure. We did not systematically review these data in our study subjects because of a concern of multiple confounders.

Oxygen desaturation to 85% was seen mostly in children < 20 kg, and of those that did experience the desaturation, a significantly larger amount of propofol was given. Desaturation during EGD can happen for many reasons including but not limited to apnea, coughing, respiratory depression or undiagnosed upper respiratory infection. Smaller children, in general, have decreased functional residual capacity and therefore are more likely to desaturate under these conditions. This may account for the fact that desaturation was seen mostly in the lower weight children. The oxygen desaturation generally responded to an increase in nasal cannula oxygen flow, chin lift or jaw thrust and as noted above further intervention was unusual. Of the total of 675 patients studied 19 (3%) required limited bag-mask ventilation because of oxygen desaturation and none required intubation. Additional future investigations should be performed looking at the specific reasons for desaturation with respect to propofol dosing, premedication with midazolam, and strategies to minimize this problem.

The main strength of our study is its standardization of prospective data collection on a large number of children undergoing EGD reflecting real world experience. However, we recognize several limitations as well. The effect of intravenous lidocaine given prior to propofol to blunt cough may have affected dosing schedules. The use of concomitant fentanyl was unusual in our patients (6%) as was noted in a previous report of propofol use for EGD in children [6]. Interestingly the mean total propofol dose per procedure was 6.2 mg/kg in our patients compared to 6.8 mg/kg in the other series [6], though the mean procedure time in our patients of 4.7 ± 1.2 min was considerably shorter than the 7.1 ± 3.5 minutes reported in the other. The synergistic effects of fentanyl and propofol have been shown to lower propofol requirements for EGD [1].

In conclusion, our study shows that higher induction and total doses on a mg/kg basis of propofol are needed for EGD in smaller weight children. Moreover, patients with higher BMI (overweight/obese) needed lower propofol dosing (mg/kg) than those with normal BMI. Clinicians need to be aware that pre-EGD midazolam decreases the propofol induction dose requirement and that care should be taken in not overdosing propofol in these patients. This information will be useful to clinicians unfamiliar with sedation needs for EGD in children and provides a frame of reference for safe care.

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