Safety and Efficacy of Pediatric Sedation Protocols for Painless Diagnostic Examination in A Pediatric Emergency Room of A Single Tertiary Hospital

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Abstract

Background: Pediatric patients undergoing diagnostic tests in the pediatric emergency room are frequently sedated. Although efforts are made to prevent adverse events, no sedation protocol has specified the optimal regimen, dosage, and interval of medication to prevent adverse events. This study analyzed the safety and efficacy of sequential pediatric sedation protocols for pediatric patients undergoing diagnostic tests in the pediatric emergency room of a single tertiary medical center.

Methods: The medical records of patients aged <18 years who visited the pediatric emergency room of Seoul Asan Medical Center between January and December 2019 for diagnostic testing were retrospectively reviewed. Sedation protocols consisted of 50 and 25 mg/kg chloral hydrate, 0.1 and 0.1 mg/kg midazolam, and 1 and 0.5–1 mg/kg ketamine, administered sequentially at intervals of 30, 20, 10, 10, and 10 min, respectively. Patients were assessed prior to sedation, and adverse events were investigated.

Results: Of the 289 included patients, 20 (6.9%) experienced adverse events, none serious, and nine (3.1%) failed to reach the depth of sedation required to complete the test. The regimen (P=0.622) and dosage (P=0.777) of the sedatives were unrelated to the occurrence of adverse events when sedation was performed according to protocol.

Conclusion: The sedation protocol used in these patients, consisting of sequential administration of minimum dosages, achieved a sufficient depth of sedation with relatively few adverse events, indicating that this protocol can be used safely and effectively for painless sedation in pediatric patients undergoing diagnostic testing.

Introduction

Due to their fear and anxiety, pediatric patients undergoing examination and treatment are often less cooperative than adults, even when examinations and treatments are painless. In addition, children frequently present with ambiguous symptoms and signs that require diagnostic tests. Sedation is therefore often required for the examination and treatment of uncooperative children [1]. Moreover, sedation in the emergency department (ED) is being more frequently administered by emergency department doctors, rather than by anesthesiologists, indicating the need for a safe sedation protocol [2].

Sedation, however, can be accompanied by adverse events (AE), the most frequent being respiratory suppression and vomiting [3]. Other AEs can include low blood pressure, bradycardia, and myoclonus, which can sometimes be serious [3]. Sedation-associated AE rates can be as high as 11%, with 1% being serious [3, 4]. Studies have sought to identify risk factors predictive of these AEs [3, 5], and efforts to minimize their occurrence have involved presedative assessment and intrasedative monitoring [6, 7]. However, the type of sedation administered to pediatric patients in the ED has been found to depend on the patient's condition, the situation inside the ED, and the skill and preference of the physician, preventing control of AEs. As a result, different regimens and doses of medications are administered in

different facilities and to different patients [1]. At present, therefore, there are few guidelines regarding the safe administration of sedatives, including their regimens and dosage, and interval of drugs, to pediatric patients in the ED. This retrospective study therefore evaluated the efficacy and AEs of a sedation protocol already in use in the pediatric ED of a single tertiary hospital.

Methods

Study design, setting, participants

The medical records of patients aged <18 years who visited the pediatric emergency room of Seoul Asan Medical Center between January and December 2019, and were sedated for diagnostic testing, were reviewed. Patients who required advanced airway interventions, such as tracheostomy or endotracheal intubation, before the test were excluded. This study was approved by the institutional review board of the Asan Medical Center, Seoul, Korea (IRB number: 2020–1635). All methods were performed in accordance with the relevant guidelines and regulations by including a statement in the Methods section.

Baseline demographic and clinical characteristics were recorded, including patient age and gender; results of presedative assessment; sedative regimens, including types and dosages of sedative agents and intervals between doses; and vital signs, level of consciousness, and AEs during sedation. The type of tests conducted during sedation and patient diagnosis determined by the examination were investigated.

Sedation protocol

All patients and/or their parents provided written informed consent after the purpose and method of sedation, and its possible AEs, were explained to them. Prior to sedation, patients' vital signs, oxygen saturation, weight, age, predicted diagnosis, test modality, dental condition, signs of upper airway obstruction, modified Mallampati score [8], and American Society of Anesthesiologists (ASA) physical status [9] were determined. Patients with sedation-associated risk factors for AEs or their parents were required to sign an augmented informed consent form and were carefully monitored during sedation. A percutaneous oxygen saturation monitor was attached to each patient, and a portable oxygen tank, oxygen supply tools, and airway devices were prepared.

A standardized sedation protocol was formulated by physicians in the anesthesiology and pediatrics departments, and was based on the pharmacokinetics and pharmacodynamics of chloral hydrate, midazolam, and ketamine (Fig. 1). The dosage and usage of all sedatives were checked twice with the nurse or doctor in the ED. Per oral (PO) chloral hydrate 50 mg/kg was administered, and the patient was monitored for 30 min. If PO administration was not possible, intravenous (IV) drugs were administered initially. If the depth of sedation was suboptimal, 25 mg/kg PO chloral hydrate, IV midazolam 0.1 mg/kg (maximum 3 mg), and IV midazolam 0.1 mg/kg (maximum 2 mg) were administered sequentially, with observation periods of 20, 10, and 10 min, respectively. If the required depth of sedation was not attained,

IV ketamine doses of 1 and 0.5–1 mg/kg were administered sequentially at 10 min intervals. If the depth of sedation remained suboptimal, the test was postponed, or an anesthesiologist was consulted.

Definitions

This study utilized standardized definitions from the Quebec Guidelines, a consensus-based document developed by North American experts in pediatric procedural sedation, as well as general medical terms [10]. Head concussion was defined as a traumatic head injury that temporarily affected brain function, including loss of consciousness, vomiting, and lethargy. Dental abnormalities were defined as abnormalities of the teeth, jaw, or oropharynx that could prevent mouth opening or obstruct the airways. Upper airway obstructions were defined as those with a potential for airway complications, including tracheomalacia, laryngomalacia, congenital anomalies of the airways and neck, sleep apnea, and severe snoring. The duration of sedation was defined as the time from the administration of the first sedative to physiologic recovery. ED recovery was defined as the time from the end of sedation to physiologic recovery state allowing safe discharge from the ED.

Adverse events

Hypopnea was defined as oxygen desaturation requiring airway repositioning, oxygen administration, or increased oxygen, without the need for vigorous tactile stimulation or positive pressure ventilation. Apnea was defined as oxygen desaturation requiring administration of reversal agents, vigorous tactile stimulation, or positive pressure ventilation. Vomiting was defined as the expulsion of gastric contents through the mouth or nose during the induction or maintenance of sedation or during recovery in the ED. Hypotension was defined as systolic blood pressure (BP) <90 mm Hg, mean arterial pressure <70 mm Hg, <5th percentile for age, or systolic BP <2 standard deviations (SDs) below normal for age. Pre-hypotension was defined as BP lower than initially observed but not corresponding to the definition of hypotension. A paradoxical response was defined as unanticipated restlessness or agitation in response to the administration of sedative drugs during sedation. Myoclonus was defined as involuntary, brief contractions of some muscle fibers, of an entire muscle, or of several muscles in one group, leading to movements of the corresponding body parts, but usually lasting <100 milliseconds [11]. Serious AEs included apnea, laryngospasm, hypotension, bradycardia, complete airway obstruction, clinically apparent pulmonary aspiration, permanent neurologic injury, or death, requiring significant interventions. Failure to test was defined as the suspension of a test due to serious AE, or postponement of a test due to a suboptimal depth of sedation despite administration of maximum doses of sedative agents according to protocol.

Statistical analysis

Patients were categorized into groups with and without AEs. Continuous variables were compared using Mann–Whitney U-tests, and categorical variables were compared using χ-square tests. Associations of clinical characteristics with AEs were analyzed by grouping patients by regimen and sedative dosages. The total dosage was calculated by adding the following doses as a single dose: chloral hydrate, 50

mg/kg; midazolam, 0.1 mg/kg; and ketamine, 1 mg/kg. All statistical analyses were performed using PASW Statistics Version 18.

Results

During the study period, 291 patients were administered sedatives for diagnostic testing in the pediatric ED. Two patients who had already undergone a tracheostomy were excluded; thus the study consisted of 289 patients. Of these, 20 (6.9%) patients experienced an AE, whereas 269 (93.1%) did not, with no patient experiencing a serious AE. Patient demographic and clinical characteristics are summarized in Table 1. The 289 patients included 164 (56.7%) boys and 125 (43.3%) girls, of median (interquartile range [IQR]) age 2.7 (1.1–4.8) years and median (IQR) weight 13.2 (9.5–17.4) kg. Sex distribution (P=0.572), age (P=0.892), and weight (P=0.394) did not differ significantly in the AE and non-AE groups. Diagnostic tests performed under sedation included computed tomography (CT) in 175 (60.6%) patients, magnetic resonance imaging (MRI) in 76 (26.3%), ultrasonography (US) in 19 (6.6%), and electroencephalography (EEG) in 18 (6.2%), with no significant differences in the percentages of patients in the AE and non-AE groups who underwent CT (P=0.673), MRI (P=0.607), US (P=1.000), and EEG (P=0.359). Final diagnoses included head concussion in 85 (29.4%) patients, seizure in 38 (13.1%), cervical lymphadenopathy in 18 (6.2%), and tumor in 17 (5.9%), with the rate of head concussion being significantly higher in the AE than in the non-AE group (OR, 2.59; 2SD, 1.04–6.47; P=0.036).

Presedative assessment showed that rates of dental abnormality (P=0.398) and signs of upper airway obstruction (P=0.806), as well as modified Mallampati score (P=0.316) and ASA classification (P=0.705), did not differ significantly in the AE and non-AE groups (Table 2). Median (IQR) sedation and ED recovery time were 94 (66–142.3) and 87 (57–114.8) min, respectively, with no significant differences between the AE and non-AE groups. Of the 20 patients with AEs, hypopnea was the most frequent, being observed in 11 (55%) patients, followed by vomiting, pre-hypotension, paradoxical response, and myoclonus. Tests could not be performed in nine (3.1%) because of suboptimal depth of sedation despite full administration of sedatives.

Categorization of patients into five groups based on sedative regimens showed that patients sedated with chloral hydrate + midazolam had the highest rate of AEs (3/28, 10.7%) and that patients sedated with a single dose of midazolam had the lowest rate (0%), but there was no statistically significant differences between pairs of groups (Figure 2, Appendix 1). Categorization of patients into five groups based on sedative doses showed no relationship between sedative dose and rate of AEs (P=0.777) (Fig. 3).

Discussion

The protocol used in this study was relatively safe and could achieve a sufficient depth of sedation. The overall AE rate was 6.9%, equal to or lower than previously reported, with none of the patients in the present study experiencing a serious AE [4, 12-14]. The failure rate of sedation for diagnostic tests in the

pediatric ED has been reported to be as high as 8% [15]. In comparison, the protocol tested in this study induced a sufficient depth of sedation in 96.9% of patients, enabling diagnostic tests to be successfully performed.

Of the 289 pediatric patients, 176 (60.9%) were sedated with chloral hydrate; of the latter, 164 (93.2%) attained an optimal depth of sedation without an AE. Chloral hydrate is a traditional sedative that has been used in pediatric EDs for several decades [16-18]. This widely used agent has been found to be safe and effective [18-21], although AEs such as oxygen desaturation and vomiting are relatively frequent [18]. In addition, the long half-life of chloral hydrate increases the risk of resedation [15, 22], and the test failure rate is about 5–8% [15]. When administered according to the study protocol, chloral hydrate was safe and effective, and IV access was minimized to prevent unnecessary pain or fear in the patient. These findings suggest that the usefulness of chloral hydrate for sedation is dependent on the treatment protocol. Although this study found that orally administered choral hydrate was safe, implementation of a non-invasive modality requires a relatively clear dose–response relationship, an agent with a short half-life, and fewer AEs such as vomiting [23-27]. Large-scale, prospective multi-center studies are needed to establish the safety and efficacy of oral chloral hydrate in pediatric patients undergoing sedation for diagnostic testing.

Although the rates of AEs did not differ significantly for most diagnoses, the rate of head concussion was significantly higher in the AE than in the non-AE group (OR 2.59; 2 SD, 1.04–6.47; P=0.036). A concussion is a traumatic brain injury accompanied by loss of consciousness or neurological abnormalities that can cause respiratory dysfunction. Thus, concussion can directly affect the respiratory center, increasing the incidence of hypopnea [28].

The Mallampati score, a classical measure of pre-anesthesia assessment, did not differ significantly in the AE and non-AE groups. This finding was in agreement with studies showing that Mallampati score did not significantly predict the occurrence of AEs in pediatric patients undergoing sedation [29, 30]. Mallampati score, however, is difficult to assess objectively, as independent observers commonly grade these scores differently [30], with its reliability being especially low in patients aged <3 years [31]. The median (IQR) age of patients in the present study was 2.7 (11.1–4.8) years, suggesting a lower association between Mallampati score and AEs. Airway assessment tools that are more standardized and effective than the Mallampati score for pediatric sedation are therefore necessary.

ASA classification did not differ significantly between the AE and non-AE groups. Higher rates of AEs have been observed in pediatric patients of ASA class III and higher [32, 33]. Because almost all patients (286/289, 98.9%) in the present study were categorized as ASA class I–II, it was difficult to predict AE risk by evaluating ASA classification. Similarly, a recent study on pediatric ED sedation, with 99.7% of patients categorized as ASA class I–II, found that ASA classification was not a statistically significant risk factor for occurrence of AEs and serious AEs [3]. Children who visit the pediatric ED with acute symptoms are relatively healthy, resulting in a different patient distribution and results than in large studies of non-ED patients [34, 35]. ASA class I–II patients should therefore be targeted when evaluating sedation protocols

in a pediatric ED. The ASA classification system also has been shown to have poor inter-rater reliability due to its subjective definitions, which may have affected our study result [36]. Therefore, efforts are needed to reduce inter-rater variability, and studies are needed to reflect usual distributions of pediatric ED patients.

The advantage of this study protocol was that low-dose drugs were administered sequentially while continuously monitoring each patient's sedation status. As needed, additional doses were administered at appropriate time intervals to reduce AEs while achieving the desired depth of sedation. Administration of low doses of a single drug was successful at attaining proper depth of sedation in 67.7% of patients and low doses. By contrast, other studies found that two or more sedatives were often required [37, 38], and higher doses of these drugs were administered [12-15, 38-40]. An overly high dose can increase the incidence of AEs, as well as hospital length of stay, whereas an overly low dose may fail to achieve the depth of sedation required for diagnostic testing. A proper balance between high and low doses may be both a safe and effective tool for sedation of pediatric patients while avoiding AEs and test failure.

The major limitations of this study included its retrospective design and its inclusion of a relatively small number of patients at a single center, which reduced the power of subgroup analyses. However, the study was relatively well designed, with a protocol fully developed by pediatricians and anesthesiologists applied to all patients equally. Moreover, patients were monitored continuously while under sedation, and AEs were recorded, enhancing the validity of study results. Another limitation was that fasting time before sedation was not assessed as a risk factor for AEs. A recent study found, however, that fasting time did not affect AE rates, with the necessary depth of sedation achieved regardless of fasting [5, 41]. The rates of vomiting and pulmonary aspiration, AEs greatly affected by fasting time, were low in this study. Another limitation was that this study did not evaluate delayed AEs, which occur after discharge from the ED. Several studies have reported that 9–15% of patients experienced AEs after ED discharge [13, 40]. Future large-scale studies should include evaluations of AE rates after ED discharge in patients administered chloral hydrate, which has a relatively long half-life (9.68 ± 7.73 h) [42]. Despite these limitations, prospective, multi-center large-scale studies that include thorough presedative assessment and continuous assessment of patients during sequential low-dose administration of sedatives may be warranted.

In conclusion, The sedation protocol used in the study, involving minimal-sequential administration of sedatives, yielded an AE rate similar to that of a single sedative in pediatric patients undergoing diagnostic testing. Moreover, this protocol resulted in a sufficient depth of sedation, indicating that it is safe for diagnostic testing.

List Of Abbreviations

emergency department, ED; adverse events, AE; American Society of Anesthesiologists, ASA; Per oral, PO; intravenous, IV; blood pressure, BP; standard deviations, SDs; interquartile range, IQR; magnetic resonance imaging, MRI; ultrasonography, US; electroencephalography, EEG.

Declarations

Ethics approval and consent to participate

- Ethics approval: This study was approved by the institutional review board of the Asan Medical Center, Seoul, Korea (IRB number: 2020–1635).
- Consent to participate: This study was a retrospective study, and the consent to participate was exempted, which was approved by the institutional review board of the Asan Medical Center, Seoul, Korea (IRB number: 2020–1635). Although consent for participation in the study was not obtained, consent for purpose, method and adverse effects of sedation described in the manuscript were obtained.

Consent for publication: Not applicable

Availability of data and materials: Not applicable

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Authors' contributions

JS Park: Drafting and critical revision of the manuscript for important intellectual content, substantial contributions to analysis, and interpretation of data

YH Byun: Substantial contributions to analysis and interpretation of data

JY Lee: Substantial contributions to acquisition of data

JS Lee: Substantial contributions to acquisition of data

JM Ryu: Substantial contributions to acquisition of data

SJ Choi: Critical revision of the manuscript for important intellectual content and final approval of the version to be published

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Tables

Table 1. Patient characteristics and clinical data				
	No adverse event	Any adverse event	Total	P value
	(n = 269)	(n = 20)	(n = 289)	
Demographics				
Sex (male)	155 (57.6)	9 (45)	164 (56.7)	0.272
Age (years)	2.7 (1.2-4.8)	3.2 (0.9-5.2)	2.7 (1.1-4.8)	0.892
Body weight (kg)	13.3 (9.8-17.6)	13 (9.1-15.1)	13.2 (9.5-17.4)	0.394
Reason for sedation				
CT	162 (60.2)	13 (65)	175 (60.6)	0.673
MRI	72 (26.8)	4 (20)	76 (26.3)	0.607
US	18 (6.7)	1 (5)	19 (6.6)	1.000
EEG	16 (5.9)	2 (10)	18 (6.2)	0.359
Biliary scan	1 (0.4)	-	1 (0.3)	-
Diagnosis				
Head concussion	75 (27.9)	10 (50)	85 (29.4)	0.036[$]
Seizure	35 (13)	3 (15)	38 (13.1)	0.735
CLAP	17 (6.3)	1 (5)	18 (6.2)	-
Tumor	17 (6.3)	-	17 (5.9)	-
Encephalopathy	12 (4.5)	-	12 (4.2)	-
AGE	10 (3.7)	-	10 (3.5)	-
CHD	10 (3.7)	-	10 (3.5)	-
KD	7 (2.6)	1 (5)	8 (2.8)	-
Meningoencephalitis	7 (2.6)	1 (5)	8 (2.8)	-
Other[*]	79 (29.4)	4 (20)	83 (28.7)	-
Results are presented as median (interquartile range) or number (%).				
Abbreviation: CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasonography; EEG, electroencephalography; CLAP, cervical lymphadenopathy; AGE; acute gastroenteritis; CHD, congenital heart disease; KD, kawasaki disease)				
[*]Other diagnosis includes fever, appendicitis, headache, hydrocephalus, septic arthritis, transient synovitis, biliary atresia, acute cerebral infarction, pneumonia, soft tissue abscess, Bell's palsy, fracture, moyamoya disease, preseptal cellulitis, acute laryngitis, joint dislocation, foreign body				

aspiration, acute hepatitis, liver cirrhosis, aortic aneurysm, optic neuritis, congenital diaphragmatic hernia, choledocal cyst, traumatic hemothorax, mechanical ileus, ophthalmologic exam, ovarian cyst torsion, pulmonary sequestration, slipped capital femoral epiphysis, thyroglossal duct cyst and torticolis.
[$]Odds ratio : 2.59 (1.04-6.47)

Table 2. Sedation details of study population					
		No adverse event	Any adverse event	Total	
		(n = 269)	(n = 20)	(n = 289)	P value
Risk factors for adverse event					
Dental abnormality		6 (2.2)	1 (5)	7 (2.4)	0.398
Upper airway obstruction sign		3 (1.1)	0 (0)	3 (1)	0.806
modified mallampati's scale	1	120 (45)	12 (60)	132 (46)	0.316
	2	148 (55)	8 (40)	156 (54)	
	3	1 (0.4)	0 (0)	1 (0.3)	
	4	0 (0)	0 (0)	0 (0)	
ASA class	1	152 (57)	13 (65)	165 (57)	0.705
	2	114 (42)	7 (35)	121 (42)	
	3	3 (1.1)	0 (0)	3 (1)	
	4	0 (0)	0 (0)	0 (0)	
	5	0 (0)	0 (0)	0 (0)	
Sedation time					
Sedation duration (min)		110 (75-160)	113 (75-164)	94 (66-142.3)	0.346
ED recovery (min)		100 (60-141)	100 (61-144)	87 (57-114.8)	0.161
Adverse event*					
Hypopnea			11 (55)		
Vomiting			4 (20)		
Pre-hypotension			2 (10)		
Paradoxical response			2 (10)		
Myoclonus			1 (5)		
Failure to test		9 (3.3)	0 (0)	9 (3.1)	-
Results are presented as median (interquartile range) or number (%).					
Abbreviation: ASA, American Society of Anesthesiologists Classification; ED, emergency department.					

*No record for event that didn't happen (e.g., apnea, bradycardia, pulmonary aspiration, seizure, death etc.)

Figures

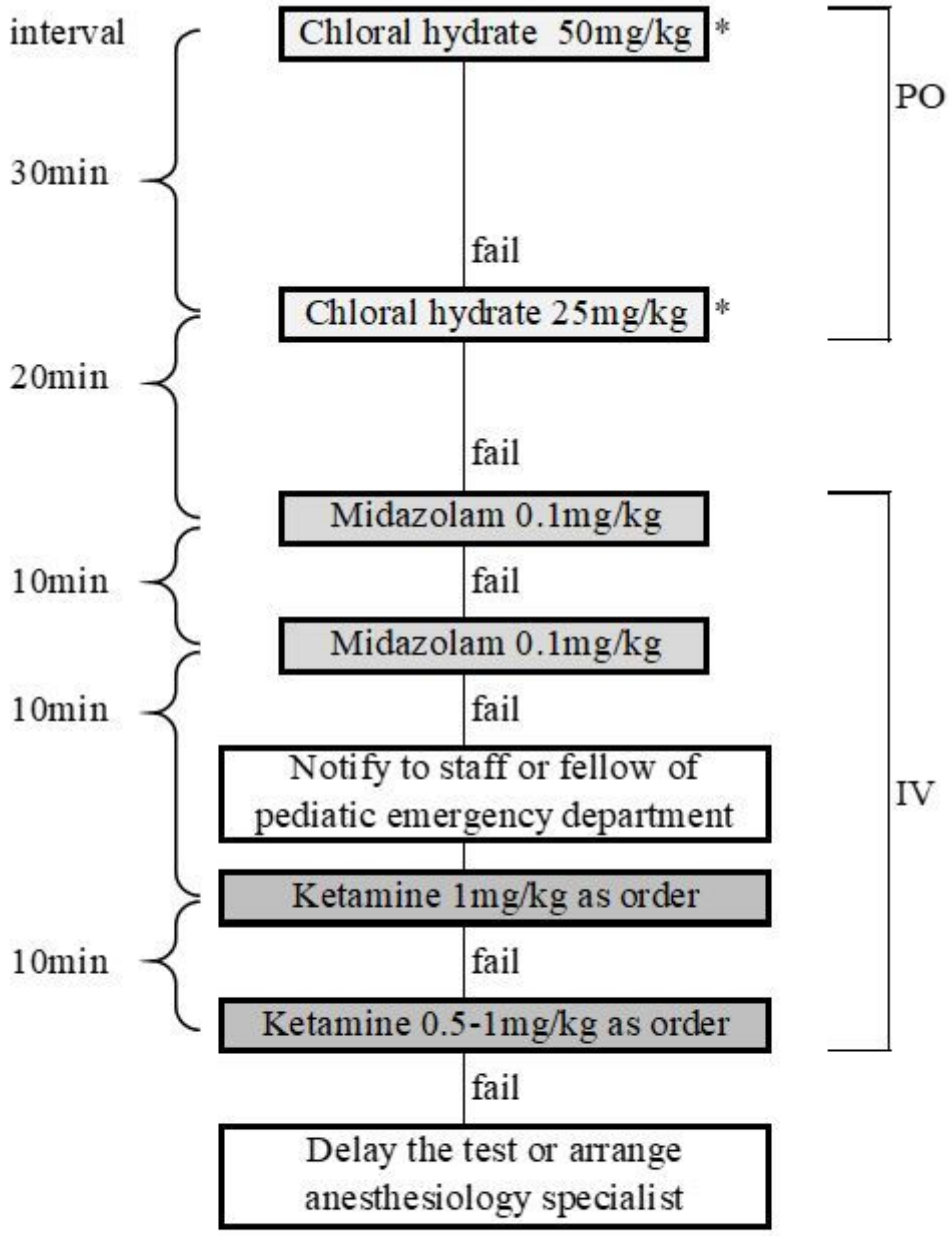
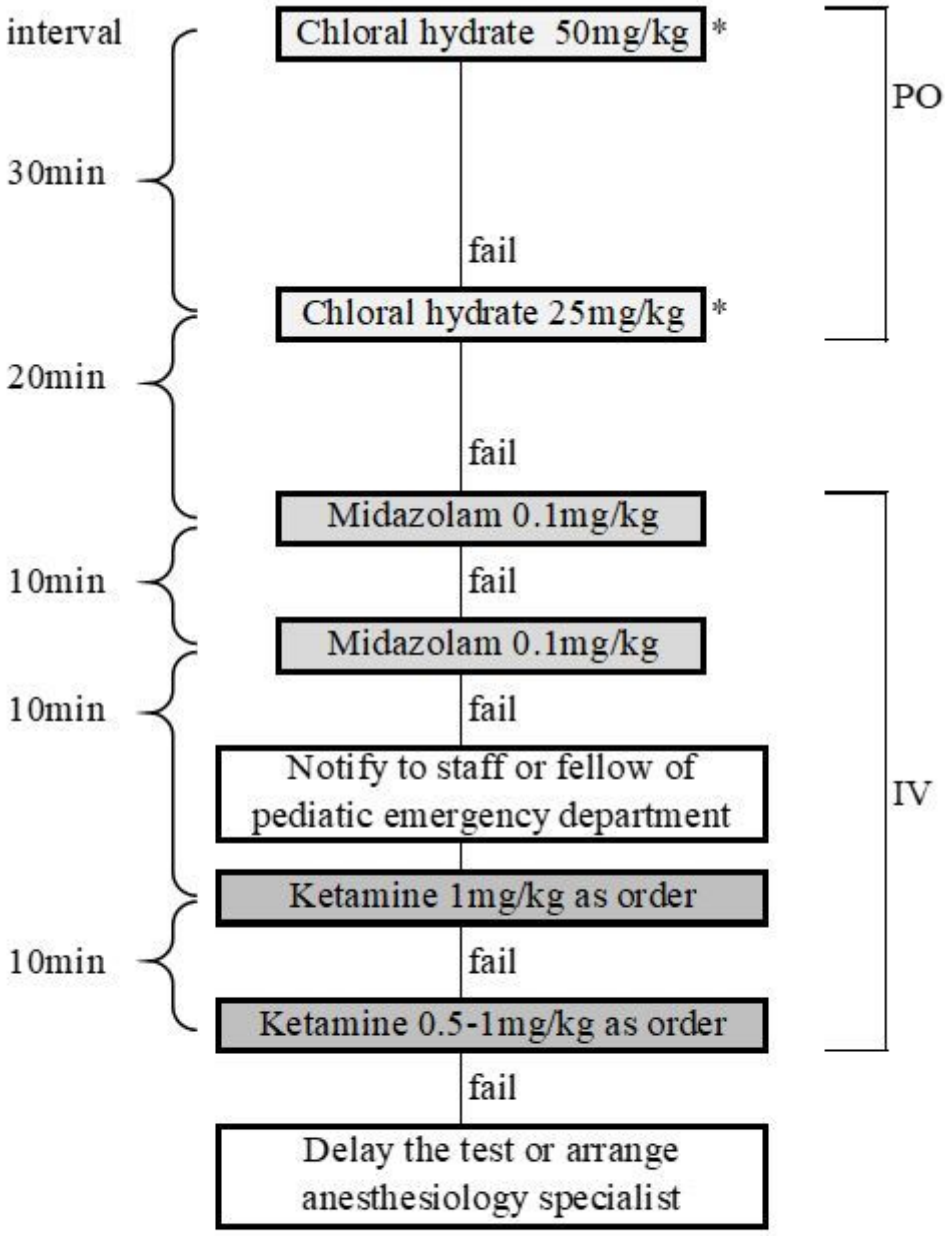


Figure 1

Sedation Protocol used for study population



Abbreviations: PO, per oral; IV, intravenous.
* If oral intake is not possible, IV drugs can be used initially

Figure 1

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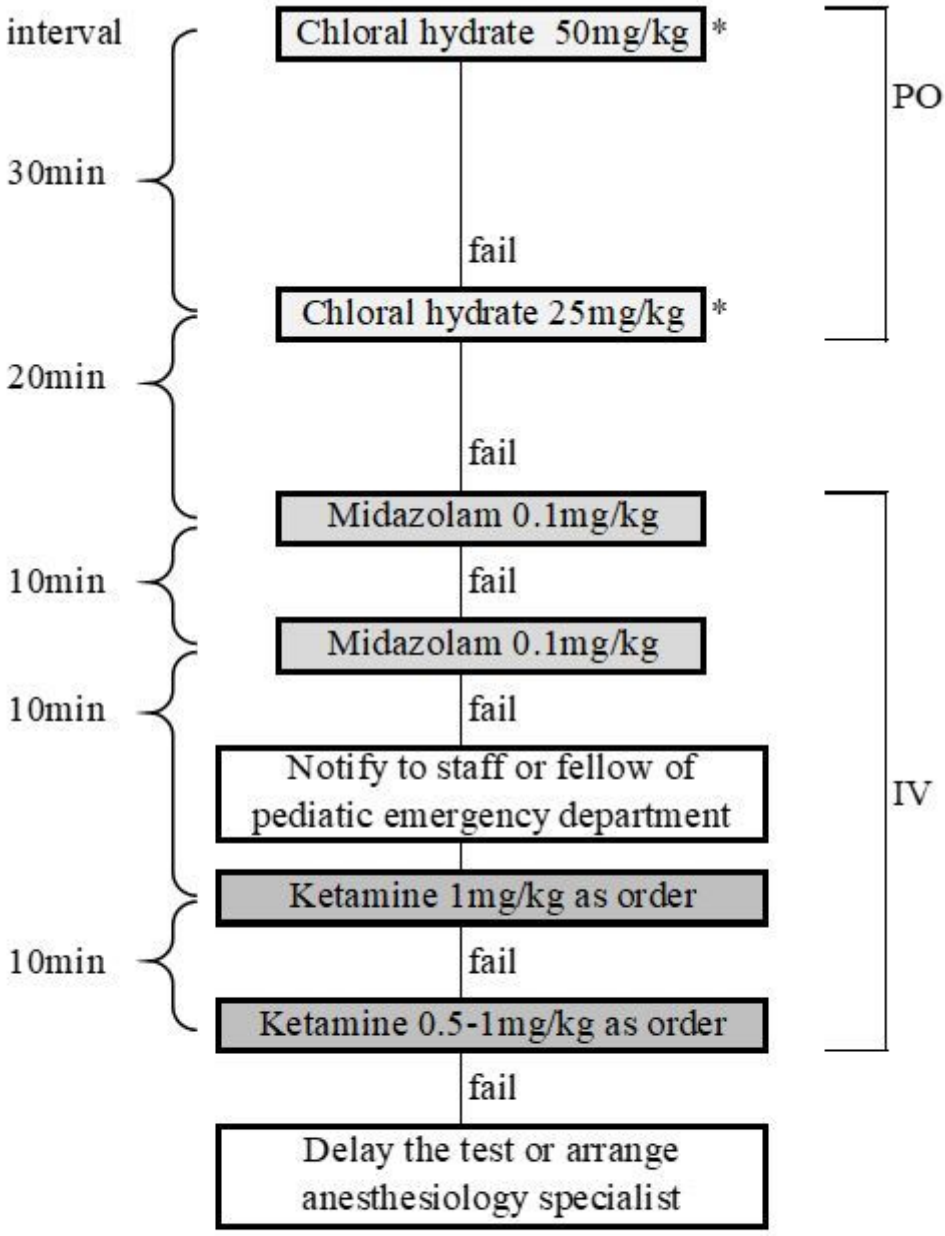

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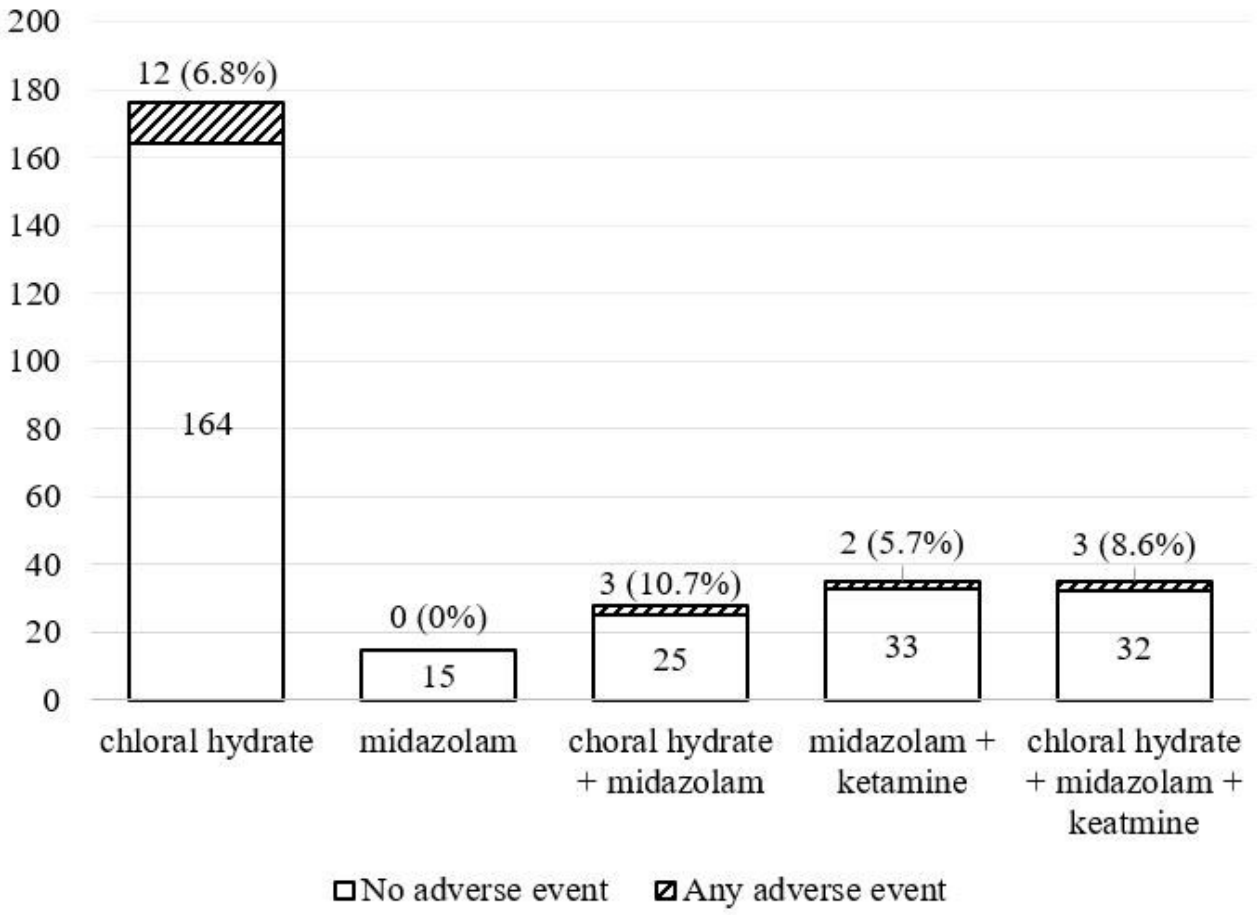
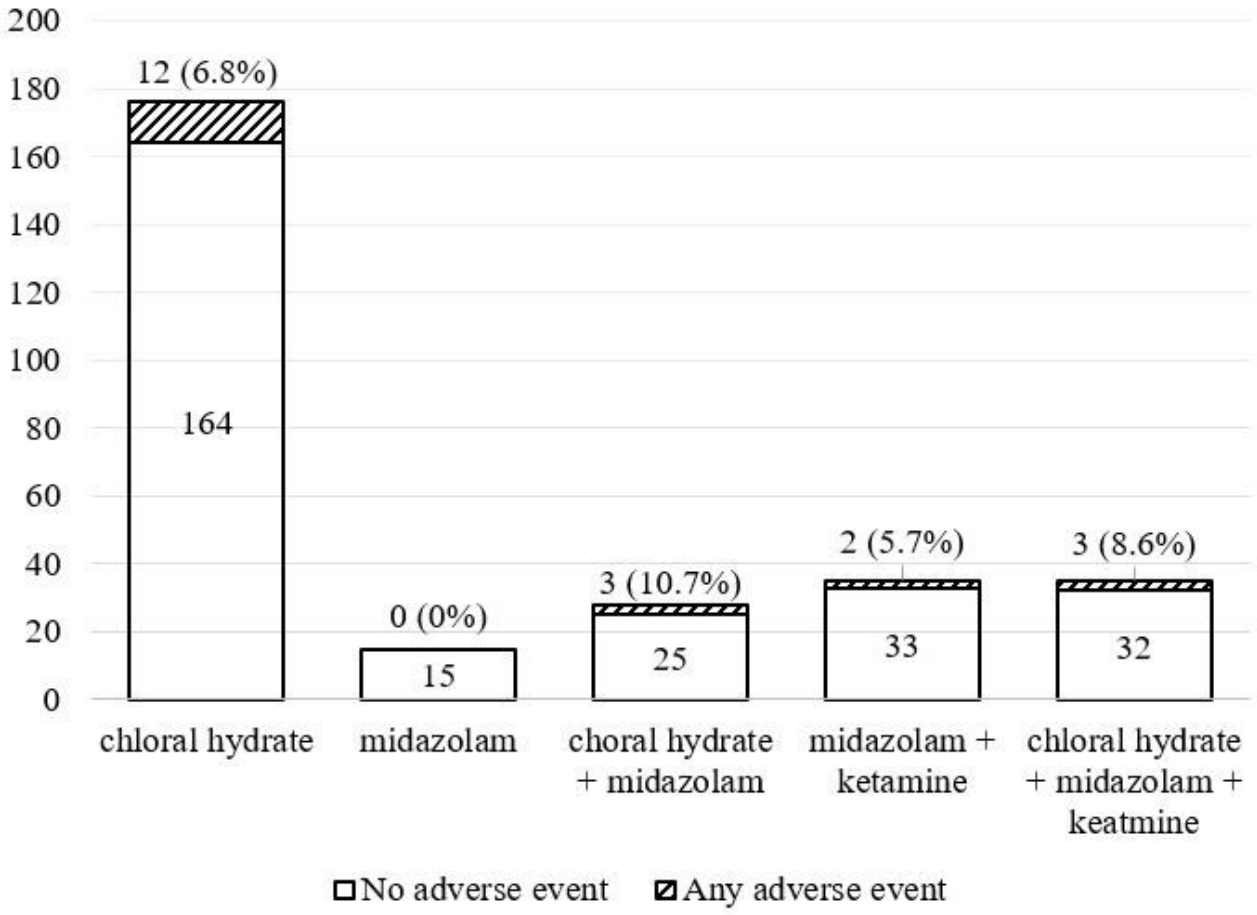


	No adverse event (n = 269)	Any adverse event (n = 20)	Total (n = 289)	P value
Chloral hydrate	164 (93.2)	12 (6.8)	176 (60.9)	0.741
Midazolam	15 (100)	0 (0)	15 (5.2)	
Choral hydrate + midazolam	25 (89.3)	3 (10.7)	28 (9.7)	
Midazolam + ketamine	33 (94.3)	2 (5.7)	35 (12.1)	
Chloral hydrate + midazolam + ketamine	32 (91.4)	3 (8.6)	35 (12.1)	

No statstical significance among each groups (Appendix 1)

Figure 2

Comparison of adverse event by sedation medication



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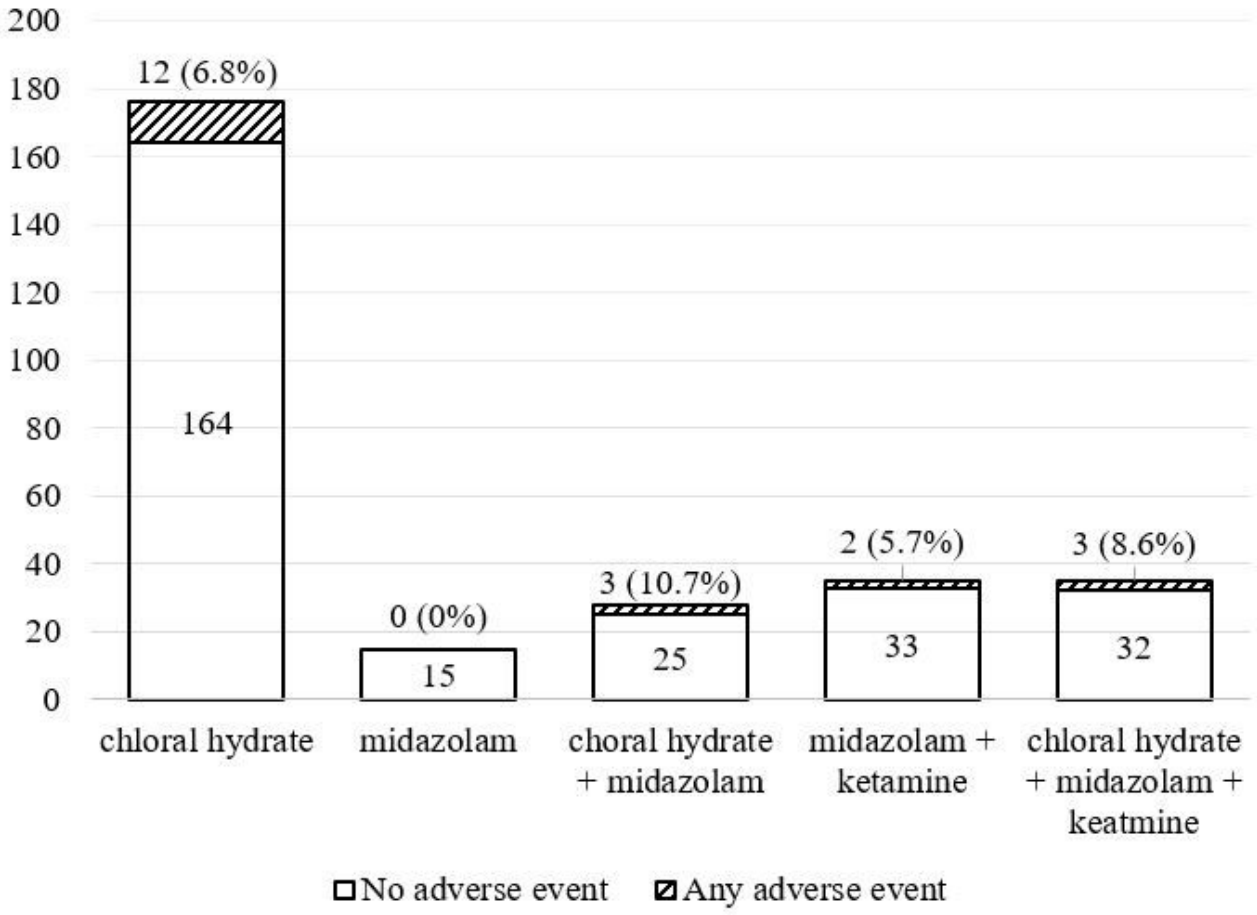

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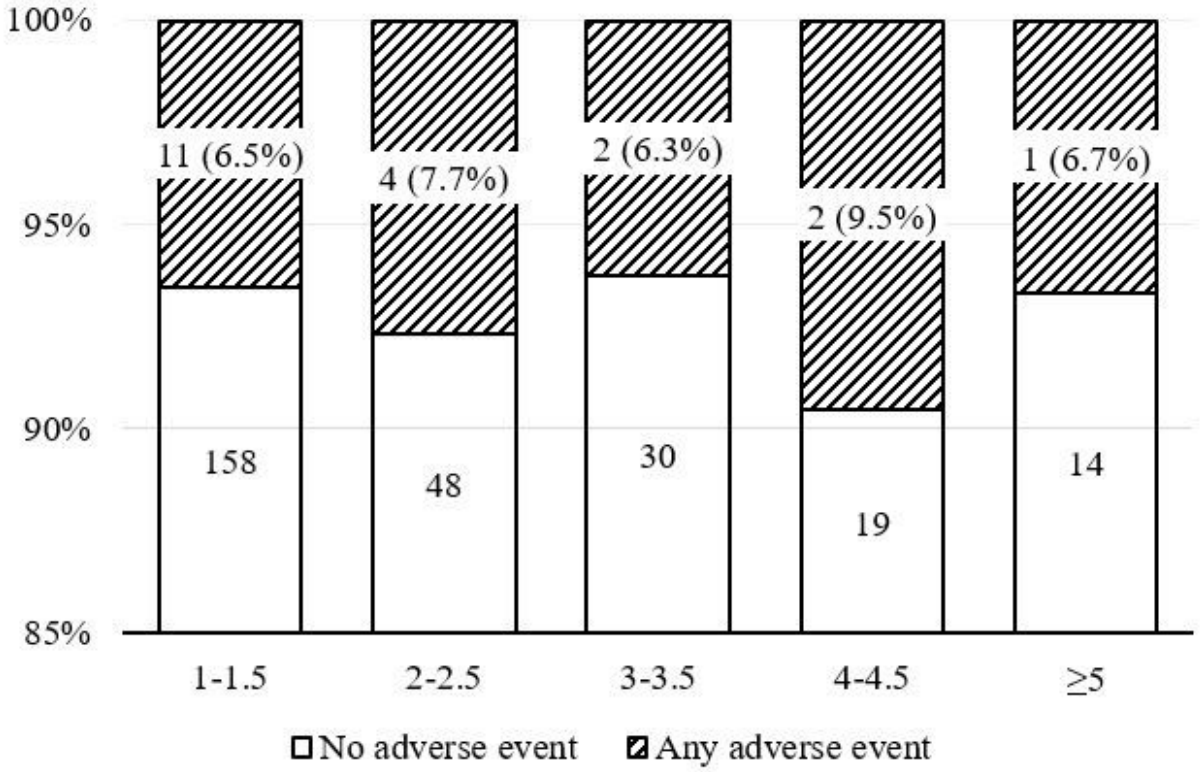


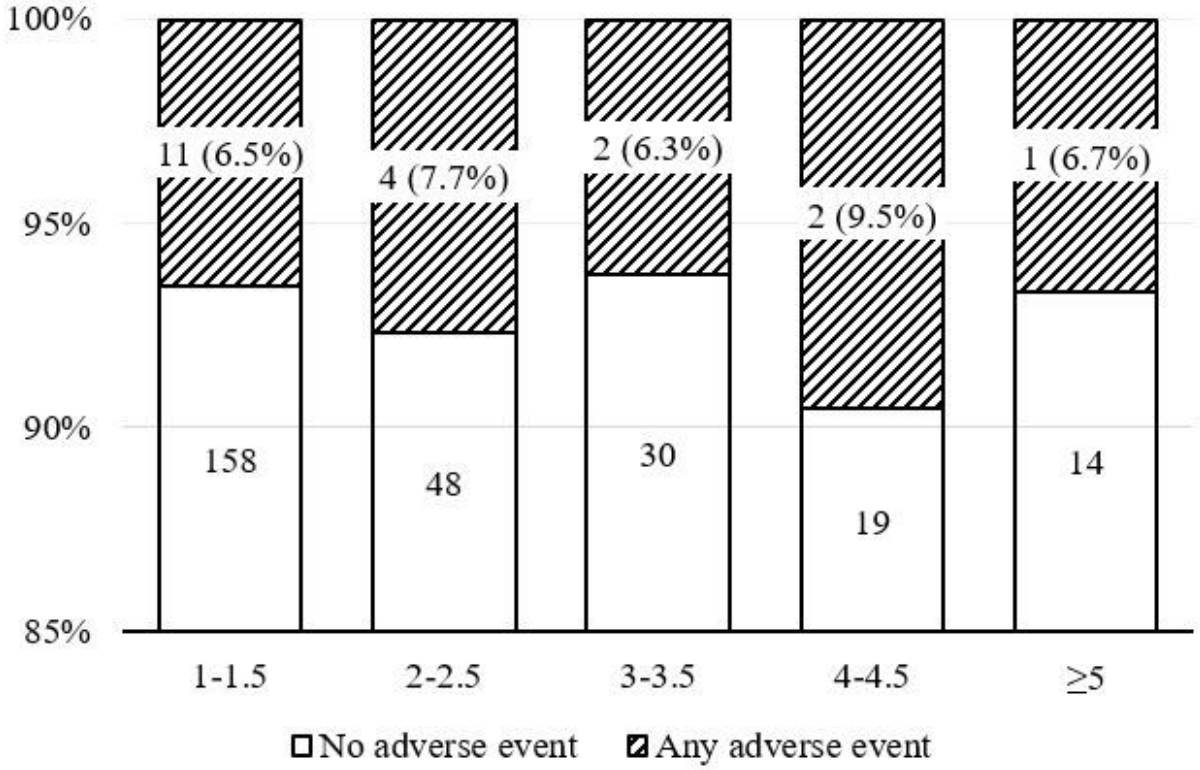
Dose*	No adverse event (n = 269)	Any adverse event (n = 20)	Total (n = 289)
1-1.5	158 (93.5%)	11 (6.5%)	169
2-2.5	48 (92.3%)	4 (7.7%)	52
3-3.5	30 (93.8%)	2 (6.3%)	32
4-4.5	19 (90.5%)	2 (9.5%)	21
≥5	14 (93.3%)	1 (6.7%)	15

*The total dosage was calculated by considering the following doses as 1dose for each type of medication; chloral hydrate. 50mg/kg; midazolam, 0.1mg/kg; ketamine, 1mg/kg.

Linear by linear association = 0.777

Figure 3

Association between adverse event and sedation dosage



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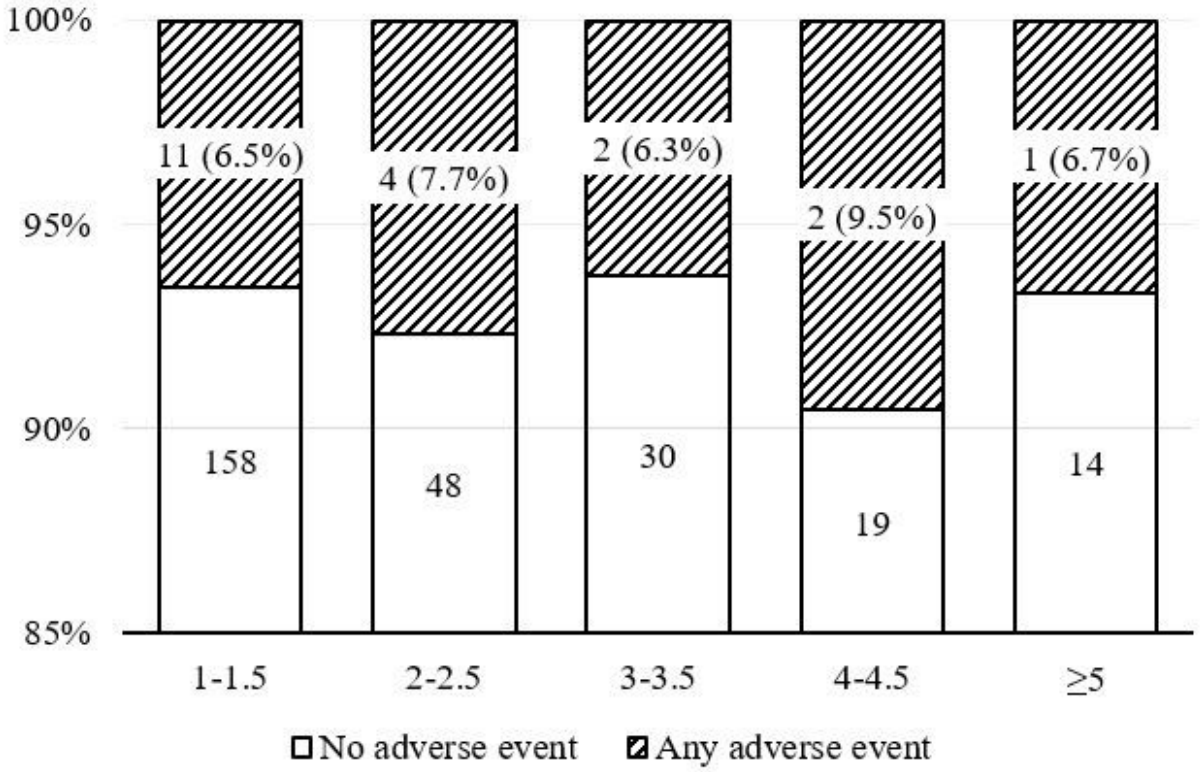

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Supplementary Files

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