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Risk factors for chloral hydrate sedation failure in pediatric patients: a retrospective analysis

Young-Eun Jang, Jung-Bin Park, Pyoyoon Kang, Sang-Hwan Ji, Eun-Hee Kim, Ji-Hyun Lee, Hee-Soo Kim, Jin-Tae Kim

Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

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Corresponding author:
Jin-Tae Kim, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-3661
Fax: +82-2-745-5587
Email: jintae73@snu.ac.kr; jintae73@gmail.com
ORCID: https://orcid.org/0000-0002-3738-0081

Background: This study aimed to investigate the risk factors for chloral hydrate sedation failure and complications in a tertiary children's hospital in South Korea.

Methods: A retrospective analysis of pediatric procedural sedation with chloral hydrate between January 1, 2021, and March 30, 2022, was performed. The collected data included patient characteristics, sedation history, and procedure. Multivariable regression analysis was performed to identify the risk factors for procedural sedation failure and complications.

Results: A total of 6,691 procedural sedation were included in the analysis; sedation failure following chloral hydrate (50 mg/kg) occurred in 1,457 patients (21.8%) and was associated with a higher rate of overall complications compared to those with successful sedation (17.5% [225/1457] vs. 6.2% [322/5234]; P < 0.001, odds ratio: 3.236). In the multivariable regression analysis, the following factors were associated with increased risk of sedation failure: general ward or intensive care unit inpatient (compared with outpatient); congenital syndrome; oxygen dependency; history of sedation failure or complications with chloral hydrate; procedure more than 60 min; and magnetic resonance imaging, radiotherapy, or procedures with painful or intense stimuli (all P values < 0.05). Factors contributing to the complications included general ward inpatient, congenital syndromes, congenital heart disease, preterm birth, oxygen dependency, history of complications with chloral hydrate, and current sedation failure with chloral hydrate (all P values < 0.05).

Conclusions: To achieve successful sedation with chloral hydrate, the patient's sedation history, risk factors, and the type and duration of the procedure should be considered.

Keywords: Chloral hydrate; Conscious sedation; Deep sedation; Drug-related side effects and adverse reactions; Hypnotics and sedatives; Pediatrics.

Introduction

Procedural sedation is increasingly used to decrease anxiety, fear, or pain during diagnostic examinations and procedures. This is an essential aspect of clinical practice for pediatric patients who cannot cooperate. Intravenous (IV) anesthetics such as midazolam, ketamine, propofol, and dexmedetomidine can be used for pediatric sedation. However, most patients requiring procedural sedation attend outpatient clinics and IV access is not established [1]. For these patients, non-IV routes, such as oral, intramuscular, or intranasal administration, are used.

Historically, the most widely used non-IV sedative is oral chloral hydrate syrup. However, its use presents considerable challenges due to slow onset of action, prolonged sedation, and high incidence of gastrointestinal side effects (nausea and vomiting) that limit

sedation success rate and result in complications such as respiratory depression, oxygen desaturation, and even death [2–5]. Chloral hydrate has not been produced in the United States since 2012.

Nevertheless, chloral hydrate is widely used for pediatric sedation in South Korea [6–9]. Despite the availability of alternative options [2,7,10–18], many hospitals continue to use oral chloral hydrate because of its low cost and its familiarity among medical staff [1,6]. If chloral hydrate is shown to have a low success rate or significant side effects in a given patient population or procedure, replacement of the sedative is appropriate. Therefore, to ensure safe and effective sedation, it is important to examine the success rate and side effects of chloral hydrate sedation based on patient characteristics and the procedures involved. To the best of our knowledge, such an analysis has not been previously conducted in South Korea.

This retrospective study aimed to analyze the success rate and incidence of side effects of pediatric chloral hydrate sedation in South Korea and identify the risk factors for procedural sedation failure and sedation-related complications.

Materials and Methods

Study design and population

This study was conducted in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines and was approved by the Institutional Review Board (number H-2208-139-1353; Date of approval, September 16, 2022) of the authors' institution. The requirement for written informed consent was waived due to the retrospective study design.

Data collection

This single-center, retrospective study included pediatric patients (age < 19 years) who initially underwent procedural sedation with chloral hydrate between January 1, 2021, and March 30, 2022, at a large, tertiary pediatric hospital. The following cases were excluded due to lack of data availability: procedural sedation with incomplete records, procedural sedation overnight, and procedural sedation in the emergency room. The following information was collected for each patient from the electronic medical records: age, sex, weight, presence of a congenital syndrome (defined as a congenital disorder of the airways, respiratory system, or neuromuscular system), congenital heart disease, preterm birth (gestational age < 37 weeks), patient location (outpatient, general ward, or intensive care unit), oxygen dependency (use of oxygen when sedation was applied), and tracheostomy state. Age groups were categorized as follows: neonates (< 1 month), infants (1–12 months), toddlers (1–6 years), children (6–12 years), and adolescents (12–18 years).

The success of procedural sedation was defined as the completion of the planned procedure following the initial administration of chloral hydrate at a dose of 50 mg/kg. Procedural sedation failure was defined as the inability to achieve a stable level of sedation after the initial dose of chloral hydrate, leading to either procedure cancellation or the requirement for rescue sedation. Procedural sedation-related variables were collected: the dose of chloral hydrate, the type of procedure (angiography, bone marrow biopsy, computed tomography, electrocardiogram, echocardiography, electromyography, electroencephalography, hearing test, lumbar puncture, manometry, magnetic resonance imaging [MRI], radiotherapy, ophthalmologic examination, wound dressing or suturing, ultrasonography or needle aspiration, X-ray or fluoroscopy, or a combination of two or more of these procedures), prior sedation history (including sedation failure or complications with chloral hydrate), rescue sedation method (medication used), and duration of sedation (from sedative administration to Modified Aldrete Score > 8). Sedation-related complications were recorded and included: respiratory depression (apnea > 15 s or respiratory rate decreased more than 50% of the baseline value), desaturation (oxygen saturation [SpO_2] < 95% or decreased less than 90% of the baseline SpO_2 value), vomiting, arrhythmia, paradoxical excitation, and allergic reaction, or others.

Sedation procedure

Parents were instructed to restrict breast milk or formula for 4 h before chloral hydrate administration and solid food for 6 h before sedation to avoid aspiration and prevent the child from sleeping to increase the sedation success rate. Chloral hydrate sedation was administered by pediatric sedation nurses trained in pediatric vital sign monitoring, pediatric resuscitation, and the administration of sedatives for pediatric diagnostic and interventional procedures. Pediatric sedation nurses checked the baseline heart rate, respiratory rate, and SpO_2 before sedation. If the patient required oxygen supplementation before sedation, this was adjusted to maintain baseline SpO_2 during sedation. The initial dose of oral chloral hydrate (50 mg/kg) was prepared using a syringe and administered in divided doses to avoid nausea or vomiting. If the patient was not sedated or could not complete the procedure with the initial dose of oral chloral hydrate, rescue sedation was administered with additional oral chloral hydrate (25 mg/kg), IV midazolam (0.1–0.2 mg/kg), or IV ketamine (1– 2 mg/kg) accord-

ing to the institution's pediatric sedation protocol.

Statistical analysis

Descriptive statistics of the baseline characteristics were conducted after categorizing the groups according to sedation success or failure. Categorical variables are presented as numbers and percentages, while numerical variables are expressed as mean ± standard deviation (SD). The χ^2 test was utilized for categorical variables, and the t-test was employed for numerical variables, as appropriate. The aim of the analysis was to identify the risk factors associated with chloral hydrate procedural sedation failure and sedation-related complications. Patient characteristics and procedure-related variables were evaluated as potential risk factors.

Univariate logistic regression (LR) analysis was performed to identify the factors associated with chloral hydrate procedural sedation failure and sedation-related complications. Variables representing more than 10% (n > 669) of the total sample (n = 6,691) and variables with a success rate closest to the overall procedural sedation success rate of 78.2% (age: toddlers, patient location: outpatient, duration of procedures: < 30 min, and procedure: electroencephalography) were chosen as the reference for each category.

Based on the results from the univariate analysis, the multivariate analysis was performed using stepwise backward LR to identify the risk factors for procedural sedation failure with an initial dose of chloral hydrate (50 mg/kg) and overall sedation-related complications. Statistical analyses were performed using SPSS Statistics® version 22 (IBM Corporation). Statistical significance was defined as a two-sided P value < 0.05.

Results

A total of 6,773 pediatric procedural sedation during the study period (between January 1, 2021, and March 30, 2022) were identified. Of these, 82 patients were excluded due to incomplete data, with 6,691 patients included in the analysis. The incidence of sedation failure was 21.8% (1,457/6,691) with an initial dose of oral chloral hydrate (50 mg/kg).

Patient characteristics are shown in Table 1. There were significant differences in the proportion of age groups, patient weight, hospitalization status, presence of congenital syndrome or congenital heart disease, oxygen dependency, tracheostomy state, history of sedation failure or complications with chloral hydrate, procedure type or duration, and duration of sedation between the failed and the successful procedural sedation groups. Patient char-

Table 1. Patient Characteristics, Sedation History, and Procedures in Pediatric Patients Undergoing Chloral Hydrate Sedation

Variable	Total (n = 6,691)	Procedural success with initial dose (n = 5,234, 78.2%)	Procedural failure with initial dose (n = 1,457, 21.8%)	P value
Initial dose of chloral hydrate (mg/kg)	50.67 ± 1.84	50.67 ± 1.84	50.66 ± 1.84	0.668
Sex				0.199
M	3,766/6,691 (56.3)	2,924/5,234 (55.9)	842/1,457 (57.8)	
F	2,925/6,691 (43.7)	2,310/5,234 (44.1)	615/1,457 (42.2)	
Age				< 0.001
Neonates (< 1 mo)	205/6,691 (3.1)	121/205 (59.0)	84/205 (41.0)	
Infants (1–12 mo)	1,905/6,691 (28.5)	1,687/1,905 (88.6)	218/1,905 (11.4)	
Toddlers (1–6 yr)	3,590/6,691 (53.7)	2,761/3,590 (76.9)	829/3,590 (23.1)	
Children (6–12 yr)	639/6,691 (9.6)	408/639 (63.8)	231/639 (36.2)	
Adolescents (12–18 yr)	352/6,691 (5.3)	257/352 (73.0)	95/352 (27.0)	
Weight	13.9 ± 9.9	13.8 ± 9.5	16.1 ± 10.9	< 0.001
Patient location				< 0.001
General ward	1,657/6,691 (24.8)	1,107/1,657 (66.8)	550/1,657 (33.2)	
Outpatient	4,843/6,691 (72.4)	4,066/4,843 (84.0)	777/4,843 (16.0)	
Intensive care unit	191/6,691 (2.9)	61/191 (31.9)	130/191 (68.1)	
Congenital syndrome (yes)	881/6,691 (9.3)	649/5,234 (8.1)	232/1,457 (13.7)	< 0.001
Congenital heart disease (yes)	471/6,691 (7.0)	398/5,234 (7.6)	73/1,457 (5.0)	< 0.001
Preterm birth (yes)	255/6,691 (3.8)	192/5,234 (3.7)	63/1,457 (4.3)	0.246
Oxygen dependency (yes)	525/6,691 (7.8)	280/5,234 (5.3)	245/1,457 (16.8)	< 0.001
Tracheostomy state (yes)	42/6,691 (0.6)	27/5,234 (0.5)	15/1,457 (1.0)	0.041

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Table 1. Continued

Variable	Total (n = 6,691)	Procedural success with initial dose (n = 5,234, 78.2%)	Procedural failure with initial dose (n = 1,457, 21.8%)	P value
Previous sedation with chloral hydrate for the same procedure	2,495/6,691 (37.3)	1,899/5,234 (36.3)	596/1,457 (40.9)	< 0.001
Previous sedation failure with chloral hydrate for the same procedure (yes)	361/2,495 (14.5)	153/361 (42.4)	208/361 (57.6)	< 0.001
Previous complications with chloral hydrate for the same procedure (yes)	107/2,495 (4.3)	59/107 (55.1)	48/107 (44.9)	< 0.001
Duration of the procedure				< 0.001
< 30 min	4,210/6,691 (62.9)	3,385/4,210 (80.4)	825/4,210 (19.6)	
30–60 min	1,680/6,691 (25.1)	1,380/1,680 (82.1)	300/1,680 (17.9)	
60–90 min	601/6,691 (9.0)	369/601 (61.4)	232/601 (38.6)	
90–120 min	166/6,691 (2.5)	89/166 (53.6)	77/166 (46.4)	
> 120 min	34/6,691 (0.5)	14/34 (41.2)	20/34 (58.8)	
Procedure				< 0.001
Angiography	37/6,691 (0.5)	3/37 (8.1)	34/37 (91.9)	
Bone marrow biopsy	3/6,691 (< 0.1)	1/3 (33.3)	2/3 (66.7)	
Computed tomography	513/6,691 (7.7)	419/513 (80.7)	94/513 (18.1)	
Electrocardiogram	37/6,691 (0.6)	28/37 (75.7)	6/37 (16.2)	
Echocardiography	451/6,691 (6.7)	401/451 (88.9)	50/451 (11.1)	
Electromyography	41/6,691 (0.6)	34/41 (82.9)	7/41 (17.1)	
Electroencephalography	916/6,691 (14.4)	784/916 (85.6)	132/916 (14.4)	
Hearing test	1,204/6,691 (18.0)	1,122/1,204 (93.2)	82/1,204 (6.8)	
Lumbar puncture	21/6,691 (0.4)	3/21 (14.3)	18/21 (85.7)	
Manometry	16/6,691 (0.2)	13/16 (81.3)	4/16 (25.0)	
MRI	1,407/6,691 (21.0)	849/1,407 (60.3)	558/1,407 (39.7)	
Radiotherapy	161/6,691 (2.4)	97/161 (60.2)	64/161 (39.8)	
Ophthalmologic examination	1,315/6,691 (19.7)	1,116/1,315 (84.9)	199/1,315 (15.1)	
Wound dressing or suturing	19/6,691 (0.3)	11/19 (57.9)	8/19 (42.1)	
Ultrasonography or needle aspiration	16/6,691 (0.2)	8/16 (50.0)	8/16 (50.0)	
X-ray or fluoroscopy	3/6,691 (0.1)	1/3 (33.3)	2/3 (66.7)	
Two or more procedures	531/6,691 (7.9)	345/531 (65.0)	186/531 (35.0)	
Duration of sedation				< 0.001
< 30 min	59/6,691 (0.9)	44/59 (74.6)	15/59 (25.4)	
30–60 min	1,464/6,691 (21.9)	1,361/1,464 (93.0)	103/1,464 (7.0)	
60–90 min	2,540/6,691 (38.0)	2,193/2,540 (86.3)	347/2,540 (13.7)	
90–120 min	1,562/6,691 (23.3)	1,147/1,562 (73.4)	415/1,562 (26.6)	
> 120 min	1,066/6,691 (15.9)	489/1,066 (45.9)	577/1,066 (54.1)	

Values are presented as mean ± SD or number (%). MRI: magnetic resonance imaging.

acteristics according to complications occurring after chloral hydrate are set out in supplemental Table 1.

Patients with failed procedural sedation had a higher overall complication rate (17.5% [225/1,457]) than those with successful sedation (6.2% [324/5,234]). Respiratory depression, desaturation, vomiting, and paradoxical excitation were more common in patients with failed sedation than in those with successful sedation. This trend was observed across all age groups (Table 2).

Using multivariable regression, the following were identified as factors associated with an increased risk of sedation failure: weight, inpatient status on a general ward or intensive care unit, congenital syndrome, oxygen dependency, a history of sedation failure or complications with chloral hydrate for the same procedure, procedure duration more than 60 min, angiography, computed tomography, lumbar puncture, two or more of the aforementioned procedures, MRI, radiotherapy, ophthalmologic examination, wound dressing and suturing, ultrasonography, and needle aspiration (Table 3).

Table 2. Complications of Chloral Hydrate Sedation in Pediatric Patients

	Total (n = 6,691)	Procedural success with initial dose (n = 5,234)	Procedural failure with initial dose (n = 1,457)	P value
Overall complications	577/6691 (8.6)	322/5234 (6.2)	225/1457 (17.5)	< 0.001
Respiratory depression*	20/6691 (0.3)	11/5234 (0.2)	9/1457 (0.6)	0.025
Oxygen desaturation†	372/6691 (5.6)	203/5234 (3.9)	169/1457 (11.6)	< 0.001
Vomiting	198/6691 (3.0)	110/5234 (2.1)	88/1457 (6.0)	< 0.001
Arrhythmia	5/6691 (0.1)	3/5234 (0.1)	2/1457 (0.1)	0.299
Paradoxical excitation	18/6691 (0.3)	7/5234 (0.1)	11/1457 (0.8)	< 0.001
Allergic reaction	3/6691 (0.05)	2/5234 (0.04)	1/1457 (0.1)	0.521
Other‡	2/6691 (0.03)	2/5234 (0.04)	0 (0)	< 0.999
Overall complications by age				
Neonates (< 1 mo)	21/205 (10.2)	9/162 (5.6)	12/43 (27.9)	< 0.001
Infants (1–12 mo)	156/1905 (8.2)	86/1467 (5.9)	70/438 (16.0)	< 0.001
Toddlers (1–6 yr)	313/3590 (8.7)	188/2821 (6.7)	125/769 (16.3)	< 0.001
Children (6–12 yr)	53/639 (8.3)	24/502 (4.8)	29/137 (21.2)	< 0.001
Adolescents (12–18 yr)	34/352 (9.7)	17/285 (6.0)	17/67 (25.4)	< 0.001

Values are presented as number (%). *Respiratory depression; apnea > 15 s or respiratory rate decreased by more than 50% of the baseline value. †Desaturation; SpO_2 < 95% or decreased by less than 90% of the baseline SpO_2 value. ‡Other complications included transient, self-limited rigidity of the body (n = 2).

Multivariable regression showed that the following factors were associated with an increased risk of overall complications during chloral hydrate sedation: general ward inpatient status, congenital syndrome, congenital heart disease, preterm birth, oxygen dependency, and a history of complications or sedation failure with chloral hydrate for the same procedure (Table 4).

Rescue sedation was administered to 93% (1,351/1,457) of the patients with failed procedural sedation. The first and overall rescue sedation success rates were 89.8% (1,213/1,351) and 91.0% (1,229/1,351), respectively (Fig. 1).

Discussion

This retrospective, single-center, observational study revealed a significant incidence of procedural sedation failure with oral chloral hydrate. Risk factors for chloral hydrate sedation failure and complications associated with chloral hydrate sedation were also identified. Patients with sedation failure had higher overall complication rates than those with successful sedation at the initial dose.

Chloral hydrate has been prescribed for over a century for sedation because it is relatively safe and effective. It has been widely used for pediatric sedation due to its low cost and familiarity with the drug among healthcare professionals [19,20]. However, oral administration of chloral hydrate is challenging due to its bitter taste, often leading to nausea and vomiting that may potentially delay the onset of sedation [21]. Therefore, efficacy varies among individuals. At doses of 25–100 mg/kg for sedation induction, chloral hydrate exhibits a broad range of onset (15–45 min), duration (20–280 min), and success rate (37.4%–100%) [1]. After initial administration, the patient is usually observed for approximately 30–40 min to assess the success of sedation. Based on the present study, factors associated with successful chloral hydrate sedation include outpatient status and procedures less than 30 min. Echocardiography (88.9%) and hearing tests (93.2%) demonstrated similarly high success rates that were comparable to those of electroencephalography (85.6%, reference test). The three tests share the following characteristics: they are painless, do not take a long time, and can be successfully performed despite slight patient movement. If these conditions are met, oral chloral hydrate can be used as an initial sedative with a high success rate.

Previously, Cui et al. [21] reported risk factors associated with chloral hydrate sedation failure, including reduced dosage, increased body weight, history of previous sedation or sedation failure, and performance of multiple procedures or MRI scans. Our study further showed that sedation failure was associated with factors such as weight, general ward or intensive care unit stay, congenital syndrome, oxygen dependency, history of previous sedation failure or complications for the same procedure with chloral hydrate, procedure duration more than 60 min, and painful procedures (angiography, lumbar puncture, wound dressing, and needle aspiration) or procedures involving intense stimulus (ophthalmologic examination).

In 2012, all manufacturers in the United States voluntarily withdrew chloral hydrate from the market due to efficacy and safety concerns [22]. Animal studies have shown that high doses of chloral hydrate have genotoxic and carcinogenic effects, although the impact on humans remains uncertain [23]. Nonetheless, pedi-

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Table 3. Multivariable Analysis of the Risk Factors of Procedural Sedation Failure with Chloral Hydrate in Pediatric Patients

Variable	Univariate simple regression		Multivariable (Univariate multiple regression)	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Sex				
M	Reference			
F	0.921 (0.819, 1.036)	0.171		
Age				
Neonates (< 1 mo)	0.974 (0.689, 1.376)	0.880		
Infants (1–12 mo)	1.096 (0.959, 1.251)	0.181		
Toddlers (1–6 yr)	Reference			
Children (6–12 yr)	1.001 (0.816, 1.229)	0.991		
Adolescents (12–18 yr)	0.862 (0.653, 1.139)	0.296		
Weight (kg)	1.018 (1.013, 1.024)	< 0.001	1.036 (1.028, 1.044)	< 0.001
Patient location				
General ward	2.601 (2.289, 2.956)	< 0.001	2.377 (1.964, 2.876)	< 0.001
Outpatient	Reference		Reference	
Intensive care unit	11.186 (8.174, 15.309)	< 0.001	9.911 (6.858, 14.324)	< 0.001
Congenital syndrome (yes)	1.333 (1.133, 1.569)	< 0.001	1.232 (1.017, 1.492)	0.033
Congenital heart disease (yes)	0.643 (0.497, 0.831)	0.001	0.579 (0.426, 0.786)	< 0.001
Preterm birth (yes)	1.183 (0.884, 1.581)	0.258		
Oxygen dependency (yes)	3.581 (2.984, 4.298)	< 0.001	1.906 (1.520, 2.390)	< 0.001
Tracheostomy state (yes)	1.955 (1.037, 3.685)	0.038		
Previous sedation with chloral hydrate for the same procedure				
Previous sedation failure with chloral hydrate for the same procedure (yes)	5.501 (4.426, 6.836)	< 0.001	3.590 (2.787, 4.624)	< 0.001
Previous complication with chloral hydrate for the same procedure (yes)	2.993 (2.036, 4.401)	< 0.001	1.645 (1.008, 2.683)	0.046
Duration of the procedure				
< 30 min	Reference		Reference	
30–60 min	0.892 (0.771, 1.032)	0.125	0.836 (0.698, 1.003)	0.054
60–90 min	2.580 (2.153, 3.092)	< 0.001	2.767 (2.206, 3.472)	< 0.001
90–120 min	3.550 (2.592, 4.861)	< 0.001	4.385 (3.016, 6.376)	< 0.001
> 120 min	5.861 (2.948, 11.654)	< 0.001	6.531 (3.072, 13.887)	< 0.001
Procedure				
Angiography	67.313 (20.381, 223.321)	< 0.001	43.127 (12.681, 146.672)	< 0.001
Bone marrow biopsy	11.879 (1.070, 131.931)	0.044	5.848 (0.450, 76.009)	0.177
Computed tomography	1.332 (0.997, 1.781)	0.052	1.957 (1.382, 2.772)	< 0.001
Electrocardiogram	1.150 (0.470, 2.809)	0.760	1.729 (0.682, 4.383)	0.249
Echocardiography	0.741 (0.523, 1.048)	0.090	1.076 (0.713, 1.623)	0.727
Electromyography	1.223 (0.531, 2.816)	0.636	1.612 (0.635, 4.090)	0.315
Electroencephalography	Reference		Reference	
Hearing test	0.434 (0.325, 0.580)	< 0.001	0.848 (0.598, 1.202)	0.354
Lumbar puncture	35.636 (10.353, 122.664)	< 0.001	17.738 (4.809, 65.426)	< 0.001
Manometry	0.000 (0.000)	0.999	0.000 (0.000)	0.999
MRI	3.904 (3.154, 4.831)	< 0.001	5.044 (3.893, 6.535)	< 0.001
Radiotherapy	3.919 (2.719, 5.648)	< 0.001	3.473 (2.263, 5.329)	< 0.001
Ophthalmologic examination	1.059 (0.835, 1.344)	0.637	2.224 (1.664, 2.974)	< 0.001
Wound dressing or suturing	4.320 (1.706, 10.939)	0.002	4.957 (1.857, 13.238)	0.001
Ultrasonography or needle aspiration	5.939 (2.191, 16.099)	< 0.001	4.494 (1.590, 12.706)	0.005
X-ray or fluoroscopy	11.879 (1.070, 131.931)	0.044	12.237 (0.935, 160.172)	0.056
Two or more procedures	3.202 (2.478, 4.138)	< 0.001	2.177 (1.561, 3.037)	< 0.001

MRI: magnetic resonance imaging. N/A: not applicable.

Table 4. Multivariable Analysis of the Risk Factors for Chloral Hydrate Complications in Pediatric Patients

Variable	Univariate simple regression		Multivariable (Univariate multiple regression)	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Sex				
M	Reference			
F	0.922 (0.766, 1.096)	0.358		
Age				
Neonates (< 1 mo)	1.195 (0.750, 1.904)	0.454		
Infants (1–12 mo)	0.934 (0.764, 1.141)	0.504		
Toddlers (1–6 yr)	Reference			
Children (6–12 yr)	0.947 (0.669, 1.283)	0.725		
Adolescents (12–18 yr)	1.119 (0.772, 1.624)	0.553		
Weight (kg)	0.967 (0.955, 0.979)	< 0.001	0.970 (0.956, 0.983)	< 0.001
Patient location				
General ward	3.123 (2.515, 3.729)	< 0.001	2.421 (1.910, 3.069)	< 0.001
Outpatient	Reference		Reference	
Intensive care unit	2.427 (1.567, 3.758)	< 0.001	0.908 (0.534, 1.545)	0.722
Congenital syndrome (yes)	2.048 (1.660, 2.527)	< 0.001	2.048 (1.630, 2.574)	< 0.001
Congenital heart disease (yes)	1.543 (1.155, 2.060)	0.003	1.535 (1.094, 2.152)	0.013
Preterm birth (yes)	1.787 (1.243, 2.569)	0.002	2.098 (1.398, 3.147)	< 0.001
Oxygen dependency (yes)	29.999 (24.281, 37.064)	< 0.001	52.545 (38.437, 71.831)	< 0.001
Tracheostomy state (yes)	5.336 (2.793, 10.195)	< 0.001		
Previous sedation with chloral hydrate for the same procedure				
Previous sedation failure with chloral hydrate for the same procedure (yes)	1.069 (0.740, 1.546)	0.722		
Previous complication with chloral hydrate for the same procedure (yes)	3.160 (1.990, 5.019)	< 0.001	2.016 (1.227, 3.313)	0.006
Sedation failure with initial dose	3.219 (2.700, 3.838)	< 0.001	3.073 (2.507, 3.768)	< 0.001
Duration of procedure				
< 30 min	Reference			
30–60 min	0.904 (0.732, 1.116)	0.347		
60–90 min	1.515 (1.159, 1.981)	0.002		
90–120 min	1.333 (0.807, 2.201)	0.261		
> 120 min	2.349 (0.966, 5.710)	0.060		
Procedure				
Angiography	0.930 (0.218, 3.973)	0.922	0.243 (0.055, 1.065)	0.061
Bone marrow biopsy	8.142 (0.727, 91.232)	0.089	2.959 (0.248, 35.303)	0.391
Computed tomography	1.266 (0.820, 1.955)	0.288	0.655 (0.411, 1.043)	0.075
Electrocardiogram	1.974 (0.674, 5.778)	0.215	1.400 (0.468, 4.195)	0.547
Echocardiography	1.413 (0.910, 2.191)	0.123	0.559 (0.342, 0.912)	0.020
Electromyography	2.262 (0.852, 6.000)	0.101	1.327 (0.479, 3.675)	0.586
Electroencephalography	Reference		Reference	
Hearing test	0.990 (0.685, 1.431)	0.957	0.833 (0.558, 1.242)	0.370
Lumbar puncture	2.714 (0.775, 9.504)	0.118	0.518 (0.142, 1.896)	0.321
Manometry	N/A	0.999	0.000 (0.000)	0.999
MRI	1.367 (0.974, 1.920)	0.071	0.807 (0.557, 1.167)	0.255
Radiotherapy	4.523 (2.838, 7.208)	< 0.001	1.412 (0.847, 2.353)	0.186
Ophthalmologic examination	1.726 (1.237, 2.407)	0.001	1.466 (1.028, 2.090)	0.035
Wound dressing or suturing	0.000 (0.000)	0.998	0.000 (0.000)	0.998
Ultrasonography or needle aspiration	5.428 (1.693, 17.402)	0.004	1.457 (0.429, 4.949)	0.546
X-ray or fluoroscopy	0.000 (0.000)	0.999	0.833 (0.558, 1.242)	0.370
Two or more procedures	3.279 (2.290, 4.694)	< 0.001	1.111 (0.743, 1.663)	0.607

MRI: magnetic resonance imaging. N/A: not applicable.

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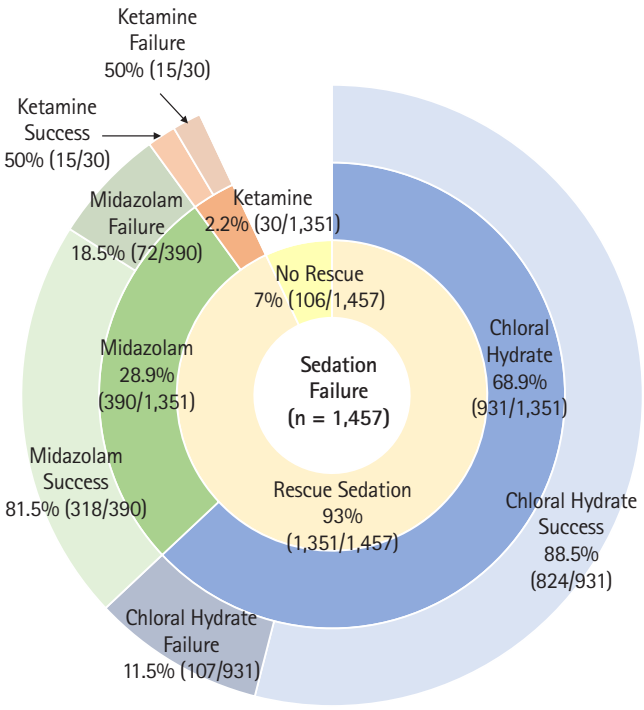

Fig. 1. The results of the first rescue sedation attempt following the initial failure of chloral hydrate sedation. Values are presented as a percentage of the total sedation failure cases (n = 1,457). The success rates of the first rescue attempt using additional chloral hydrate (25 mg/kg, n = 1,351), IV midazolam (0.1–0.2 mg/kg, n = 390), or IV ketamine (1–2 mg/kg, n = 30) were 88.5% (824/931), 81.5% (318/390), and 50% (15/30), respectively. IV: intravenous.

atric sedation in South Korea remains largely dependent on oral chloral hydrate [2,7]. According to a 2016 survey conducted by the Korean Society of Pediatric Anesthesiologists as part of the Korean guidelines for pediatric procedural sedation, 71.4% (10/14) of tertiary university hospitals reported using oral chloral hydrates as their primary sedative regardless of procedure type [24]. In addition to the variability in the effects of oral chloral hydrates, the limited availability of alternative options for non-IV sedation is a major concern. Our results showed that chloral hydrate continued to be used in patients who had previously experienced sedation failure or adverse effects with this medication. In these patients, the sedation failure rates were as high as 57.6% and 44.9%, respectively.

Another important factor contributing to the widespread use of chloral hydrate as a first-line drug for procedural sedation is the lack of specialized or dedicated pediatric sedation providers in many hospitals. For inpatients or those with IV access in place of other procedures (e.g., contrast injection for computed tomography or MRI), IV midazolam and ketamine can be used with rapid onset and short duration. However, owing to the associated risk of respiratory depression, these drugs are typically reserved for rescue sedation after failed chloral hydrate sedation. Chloral hydrate is often preferred as the first agent because it is considered safer for non-anesthesiologists who may have less experience and skills with pediatric sedation, particularly pediatric airway management. In the present study, if sedation failed after the first administration of chloral hydrate, a second dose of chloral hydrate (25 mg/kg) or IV midazolam (0.1–0.2 mg/kg) or ketamine (1–2 mg/kg) were used according to the institution's pediatric sedation protocol. However, it is important to note that when sedatives are used in conjunction with other sedatives or repeated without proper assessment, there is an increased risk of respiratory depression or hemodynamic instability. Anesthesiologists, who are proficient in the use of a variety of sedative agents, are usually involved in specific procedures such as MRI, cardiac catheterization or intervention, and gastrointestinal endoscopy that constitute only a fraction of the cases of pediatric procedural sedation. The existence of a well-structured pediatric sedation team specializing in pediatric sedation and the management of a substantial number of patients has proven to be safe and effective [25–27], In a recent meta-analysis of non-IV sedation for MRI, the authors highlighted that the presence of well-organized teams appeared to be more important than the use of a specific sedative or anesthetic regimen [1]. However, the role of a sedation team extends beyond administering sedatives and monitoring patients. The sedation team should have a good understanding of the patient's underlying disease, sedation history, and the nature of the procedure in order to select the safest and most effective sedation regimen. To prevent sedation failure and complications, it is essential to consider multiple sedation options rather than relying solely on a single type of medication, chloral hydrate, for all pediatric procedural sedation. Additionally, the sedation team should undergo regular education programs focused on delivering up-to-date evidence-based knowledge on sedative drugs and monitoring guidelines for pediatric procedural sedation.

Common side effects of chloral hydrate are nausea and vomiting (28%–37%), motor imbalance (31%–66%), restlessness (14%–29%), agitation (0.5%–29%), prolonged sedation (0.18%–30%), and drowsiness the next day (27%–35%) [4,5]. Serious complications including respiratory depression (0.2%–3.6%) [21], respiratory arrest (0.06%), and cardiac arrest (0.3%) [4] can occur, particularly when repeated doses are administered to achieve the required sedation level. The present study identified the following as risk factors for complications of chloral hydrate sedation: general ward inpatient status, congenital syndrome or congenital heart disease, preterm birth, oxygen dependency, and a history of complications or sedation failure with chloral hydrate

for the same procedure. The most common complication of chloral hydrate was desaturation, occurring in both patients with successful procedural sedation (3.9%) and patients with failed procedural sedation (11.6%). Oral administration of chloral hydrate is challenging in patients receiving oxygen supplementation, as adequate oxygenation through a face mask is compromised because of the frequent occurrence of nausea and vomiting, and of patient refusal because of the bitter taste of chloral hydrate. Delayed oral administration of chloral hydrate may lead to desaturation and hypoxemia in high-risk patients. For example, irritability and crying during oral administration can potentially trigger a right-to-left shunt in patients with uncorrected cyanotic heart disease, resulting in severe hypoxemia [28]. Additionally, due to the variability in the duration of action of oral chloral hydrate, repeated administration may result in oversedation and complications. Therefore, for procedural sedation involving these risk factors, alternative methods should be considered to increase the success rate and decrease sedation-related complications.

Dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist, exhibits sedative and analgesic properties in the pediatric population without inducing respiratory depression or neurotoxic effects. It can be administered either intranasally or intramuscularly. Therefore, dexmedetomidine is increasingly used for non-IV pediatric sedation, either as the primary sedative [1,2,10,11,13–16], as rescue sedation [12,29], or in combination with other agents such as oral chloral hydrate, intranasal midazolam [1], and intranasal ketamine [17,18]. Intranasal dexmedetomidine, administered at doses of 1–4 μg/kg, has been shown to be safe and effective in pediatric procedural sedation, without causing nasal irritation or burning pain. Intranasal administration delivers high bioavailability at 83.8%, and the low end of sedative efficacy (mean arterial plasma concentration of 100 pg/ml) can be achieved within 10 (for 2 μg/kg) to 20 min (for 1 μg/kg) [30]. Peak plasma concentrations are reached at approximately 40 min, and the sedative effects last approximately 70–80 min. Although bradycardia can occur (10%), clinically significant hypotension is rare, making dexmedetomidine a safe choice even for patients with congenital heart disease [18]. Other sedatives such as ketamine and midazolam can also be administered intranasally or intramuscularly.

Some limitations of this study should be noted. First, the data were retrospectively collected from a single tertiary pediatric center in Seoul, Korea. Therefore, institutional variations in sedative use, sedation providers, and monitoring systems were not evaluated. Second, most data were collected by the pediatric sedation nurses working in outpatient settings and general ward or intensive care unit during the daytime. Procedural sedation in the emergency room setting and overnight were provided by on-duty physicians. Sedation records in these cases were not available for the present study. Finally, detailed patient information including the American Society of Anesthesiologists' physical status classification and the severity of the underlying disease that are crucial for the assessment of sedation success and associated complications were unavailable and not included in the statistical analysis. The diagnosis and sedation records allowed verification of the presence of congenital syndrome, congenital heart disease, and oxygen dependence or preterm birth history. Despite these limitations, our study utilized comprehensive data on pediatric procedural sedation with chloral hydrate, collected at a tertiary children's hospital in South Korea.

In conclusion, oral chloral hydrate (50 mg/kg) resulted in a significant incidence of sedation failure in pediatric patients, and patients with failed sedation experienced a higher overall complication rate than those with successful sedation at the initial dose. Effective and safe sedation with oral chloral hydrate requires careful consideration of the patient's sedation history, risk factors, and procedure type and duration.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Young-Eun Jang (Conceptualization; Data curation; Formal analysis; Visualization; Writing – original draft)
Jung-Bin Park (Data curation)
Pyoyoon Kang (Validation)
Sang-Hwan Ji (Investigation)
Eun-Hee Kim (Investigation)
Ji-Hyun Lee (Investigation; Methodology)

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Hee-Soo Kim (Validation)
Jin-Tae Kim (Conceptualization; Formal analysis; Methodology; Writing – original draft)

ORCID

Young-Eun Jang, https://orcid.org/0000-0002-7511-4104
Jung-Bin Park, https://orcid.org/0000-0002-8816-5605
Pyoyoon Kang, https://orcid.org/0000-0002-1633-9426
Sang-Hwan Ji, https://orcid.org/0000-0001-6736-4464
Eun-Hee Kim, https://orcid.org/0000-0003-0697-1935
Ji-Hyun Lee, https://orcid.org/0000-0002-8384-8191
Hee-Soo Kim, https://orcid.org/0000-0002-2661-7944
Jin-Tae Kim, https://orcid.org/0000-0002-3738-0081

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