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Risk Factors on the Adverse Events of Sedation for Diagnostic Tests in Pediatric: A Retrospective Case–Control Analysis

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Abstract

Background: This report intended to identify the peri-sedation risk factors associated with the adverse events of sedation for diagnostic tests in pediatric.

Methods: This retrospective case study was approved by the local ethics committee and informed consent was waived. To investigate the risk factors for adverse events, we reviewed the medical records of 1182 pediatric patients receiving sedation from July 2016 to Oct 2021. There were 177 cases with adverse events, and approximately six control patients were identified for each case. Multivariable logistic regression was performed to identify the risk factors.

Results: 1. Oxygen desaturation and failed sedation were the most common adverse events. 2. According to univariable analysis, adverse events was associated with ASA-PS class (p=0.05), non-history of sedation (p=0.035), outpatients (p=0.048), underlying diseases (p=0.007), examination items (p<0.001), sedation plan (p<0.001), sedation medication (p<0.001). 3. Multivariable analysis showed that ASA-PS class III (OR=5.684; 95%CI 3.123-10.344); p<0.001), outpatients, non-history of sedation (OR=1.645; 95% CI 1.014-2.669; p=0.04), Circulatory system disease, CT-enhance (OR=75.534; 95%CI 27.101-210.521; p<0.001), MRI (OR=39.016; 95%CI 14.504-104.957; p<0.001), Dexmedetomidine with Propofol (OR=253.751; 95%CI 5.321-12101.526; p=0.005) and Dexmedetomidine combined Chloral hydrate with Sevoflurane (OR=109.504; 95%CI 10.598-1131.414; p<0.001) were independent factors associated with adverse events.

Conclusions: This study identified potential risk factors for adverse events in patients with sedation for diagnostic tests, that should be targeted for interventions to reduce the occurrence of the condition.

Keywords: Sedation; Adverse events; Diagnostic tests; Pediatric.

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Introduction

Children present with complex medical issues including congenital malformation, congenital heart diseases, neurologic disabilities, respiratory diseases, feeding dysfunction, and developmental delay. These comorbidities require diagnostic examination that cannot be completed without sedation or anesthesia [1-3]. With the concept of comfortable medical treatment, pediatric sedation is steadily developing for a growing number of non-invasive and painless examinations, such as CT, MRI, echocardiography, electroencephalogram and lung function. Meanwhile, the rapid growth of medical units for pediatric procedural sedation in China, and the widely ranged use of drugs and techniques in pediatric sedation, have resulted in a significant difference between sedation levels, effectiveness and associated risks [4]. Some studies have reported the sedation-related adverse event rates ranging from 6.5% to 22.02% [4-6]. There is a urgent need for specifying safety precautions to minimize the incidence of adverse events. Our sedative center is the largest sedation unit in China, provided approximately 45000 cases of procedural sedation for diagnostic tests per year.

Here, we intend to identify the risk factors for adverse sedation events in pediatric diagnostic tests through retrospective case-control study, the results of which may optimize the peri-sedation protocol.

Materials and methods

Patients received sedation for examination in our hospital between July 2016 and Oct 2021 were reviewed retrospectively for adverse events. We conducted a case–control analysis for the adverse events risk factors identification. For the case group, the patients were those identified with post-sedation adverse events. Controls were selected for patients who had underwent procedural sedation for examination without post-sedation adverse events during the same period at the same institution (About 1 month). We randomly selected six patients for every case who underwent sedation within 1 month, and Children's corresponding complete data were collected through electronic medical record system and anesthesia information system. The patients also had to meet the following inclusion criteria: age >1 day and <18 years; Sedation was given in our department; Sedation was given only once a day. We excluded cases with multiple sedation a day or the records missing. The informed consent was waived because this was a retrospective study, and this study was approved by the Ethic of Children's Hospital of Chongqing Medical University, Chongqing, China(Chairperson Professor Xu Hongmei) on 21 Mar 2022 (File NO. 2022062), a 2480 bed academic tertiary hospital, which provided approximately 45000 cases of outpatients and inpatients sedation for diagnostic tests alone per year.

Definitions

The classification and severity of adverse events are according to the TROOPS Comprehensive Research Tool [7] (www.TROOPS-sedation.com), and the adverse events are defined as the following manners [5,8]: (i) Oxygen desaturation, oxygen saturation is below 90% for more than 30 seconds. (ii) Airway obstruction, without airway interventions, and recovered by airway repositioning, supplemental oxygen, and suctioning. (iii)Apnea, no respiratory effort for greater than or equal to 20 seconds. (iv) Aspiration, digestive tract contents reflux into the airways. (v) Agitation, sustained, out of the ordinary irritability or combativeness. (vi) Arrhythmia, abnormal cardiac activity result in abnormal frequency and/or rhythm of cardiac beats, including bradycardia, as defined as heart rate 20% below the sleep heart rate for age; (vii) Delayed recovery, the time from the end of the examination to awakening is more than 2h. (viii) Failed sedation, the patient could not successfully complete the examination after sedation. (ix) Tracheal tube slip,tracheal tube slip from the trachea. (x) Unplanned admission, the outpatient is hospitalized urgently.

Data collection

The available data in the medical records included age, gender, weight, American Society of Anesthesiology Physical Status (ASA-PS), Fasting time, history of sedation, source of patients, sedation plan, sedation medication, examination items, underlying diseases, adverse events and where the patient went.

Statistical analysis

Non-normally distributed data were expressed as the median (range) and tested with the Mann–Whitney U test. Categorical data were presented as frequencies (percentages) and were analyzed with the Chi-squared test or Fisher's exact test. Multivariable logistic regression was performed to verify independent predictors for adverse events, after univariable analysis identified variables with $P<0.05$ or with clinical relevance (odds ratio [OR], 95% confidence interval [CI]). $P<0.05$ on both sides was considered statistically significant. The statistical analyses were conducted using SAS9.4.

Results

During the study from July 2016 to Oct 2021, approximately 229834 procedural sedation were implemented for examination in our sedative center. 182 adverse events were recorded, 3 cases were excluded from the analysis for not being sedated but rescued by our department, 2 cases cancelled for cough. Overall, sedation related adverse events were occurred in 177 (0.077%) patients, no adverse events occurred repeatedly on the same person. The incidence of sedation related adverse events were list in Table 1. Oxygen desaturation and failed sedation were the most common events. There were no cases of complete airway obstruction, cardiac arrest, hypotension or death. The minor adverse events were 40.10%, moderate were 35.02%, serious adverse events (SAEs) were 24.85%, comprising apnea (19 [10.73%]), arrhythmia (15 [8.47%]), aspiration (4 [2.26%]), airway spasm (4 [2.26%]) and tracheal tube slip (2 [1.13%]). There were 12 cases unplanned admissions to hospital owing to sedation related adverse events. The baseline clinical characteristics between the adverse events group and control patients were summarized in Table 2.

There was a significant difference of ASA-PS class between the adverse events and control groups ($p=0.05$), suggesting its potential as a risk factor. The higher the ASA-PS class, the higher the incidence of adverse events. The history of sedation was also observed to be different between the adverse events and control group ($p=0.035$). Patients without sedation history were higher risk (16.86%), suggesting that we should pay attention on pre-sedation evaluation. Source of patient showed

significant difference between the adverse events and control group (p=0.048). The outpatient was higher than inpatient, in concert with a higher proportion of sedation plan in intranasal combined with oral and inhalation, the most manner of sedation plan (36.11%). The underlying diseases showed significant difference between the adverse events and control group (p=0.007), suggesting its potential as a risk factor ,mainly concentrated in the respiratory (14.66%) and circulatory systems (22.68%). CT-enhance and MRI examination were the risk factor of adverse events. No differences between the adverse events and control group were detected in age and sex.

Multivariable logistic regression analysis was further performed to adjust for potential confounding factors, risk factors related to adverse events were conformed (Table 3). The ASA-PS class (OR=5.684; 95%CI 3.123-10.344); p<0.001), sedation history (OR=1.645; 95%CI 1.014-2.669; p=0.04), source of patient, underling diseases, examination items, sedation medication and sedation manners were the independent risk factors of sedation related adverse events. Compared with MRI examination, examination with CT (OR=8.104; 95%CI 2.011-32.664; p=0.003), CT-enhance (OR=75.534; 95%CI 27.101-210.521; p<0.001), ultrasound (OR=4.131; 95%CI 1.149-14.850; p=0.03), 1.5 MRI (OR=39.016; 95%CI 14.504-104.957; p<0.001)were associated with adverse events.

The medication of Dexmedetomidine combined Chloral hydrate and Sevoflurane (OR=109.504; 95%CI 10.598-1131.414; p<0.001) and Dexmedetomidine with Propofol (OR=253.751; 95%CI 5.321-12101.526; p=0.005) were the independent risk factor of sedation related adverse events. Circulatory system diseases (OR=3.981; 95%CI 1.579-10.040), outpatient (OR=3.379; 95%CI 1.873-6.097) and no sedation history (OR=1.645; 95%CI 1.014-2.669) were also significantly associated with adverse events.

Table 1: Sedation related adverse events.

Level	Adverse events	Frequency	Percent (%)
Minor (40.10%)	Oxygen desaturation	40	22.6
	Airway obstruction	14	7.91
	Allergic reaction	8	4.52
	Machine malfunction	4	2.26
	Vomiting	3	1.69
	Hyperthermia	1	0.56
	Drop of bed	1	0.56
Moderate (35.02%)	Failed sedation	31	17.51
	Delayed recovery	16	9.04
	Patient/family dissatisfied	9	5.08
	Seizure of convulsion	4	2.26
	Medication mistake	2	1.13
Serious (24.85%)	Apnea	19	10.73
	Arrhythmia	15	8.47
	Aspiration	4	2.26
	Airway spasm	4	2.26
	Tracheal tube slip	2	1.13
	Cardiac arrest	0	0
	Hypotension	0	0
	Death	0	0
Urgent Interventions	Continuous positive airway pressure	29	16.38
	CPR	12	6.78
	Intubation	9	5.08

Table 2: Baseline demographics and characteristics of patients.

Variables	Total	Adverse events		P
		No (n=1005)	Yes (n=177)	
Age, y	1.33(0.37,2.75)	1.25(0.35,2.67)	1.42(0.5,2.75)	0.372
Newborn	60(5.08)	51(85.00)	9(15.00)	0.642
<3y	870(73.60)	740(85.06)	130(14.94)	
3~6y	184(15.57)	153(83.15)	31(16.85)	
≥7y	68(5.75)	61(89.71)	7(10.29)	
Weight, kg	10(6,13.5)	10(6,13.5)	10(6.5,13)	0.924
Sex				
Male	703(59.48)	593(84.35)	110(15.65)	0.432
Female	479(40.52)	412(86.01)	67(13.99)	
ASA-PS class				
I~II	828(70.05)	715(86.35)	113(13.65)	0.05
III~	354(29.95)	290(81.92)	64(18.08)	
Fasting time, h	4.25(2.5,6.67)	4.23(2.45,6.67)	4.3(2.95,7.67)	0.194
History of sedation				
No	676(57.19)	562(83.14)	114(16.86)	0.035
Yes	506(42.81)	443(87.55)	63(12.45)	
Source of patient				
Inpatient	575(48.65)	501(87.13)	74(12.87)	0.048
Outpatient	607(51.35)	504(83.03)	103(16.97)	

Underlying diseases				
Circulatory system	194(16.41)	150(77.32)	44(22.68)	0.007
Respiratory system	266(22.50)	227(85.34)	39(14.66)	
Nervous system	326(27.58)	288(88.34)	38(11.66)	
Others	396(33.50)	340(85.86)	56(14.14)	
Examination items				
CT-enhance	110(9.31)	56(50.91)	54(49.09)	<0.001
CT	89(7.53)	79(88.76)	10(11.24)	
MRI1.5	109(9.22)	68(62.39)	41(37.61)	
MRI3.0	411(34.77)	399(97.08)	12(2.92)	
Ultrasound	304(25.72)	272(89.47)	32(10.53)	
Others	159(13.45)	131(82.39)	28(17.61)	
Sedation plan				
Intranasal+Oral+Inhalation	72(6.09)	46(63.89)	26(36.11)	<0.001
Intranasal+Oral	535(45.26)	460(85.98)	75(14.02)	
Intranasal+Inhalation	202(17.09)	179(88.61)	23(11.39)	
Intravenous	275(23.27)	231(84.00)	44(16.00)	
Inhalation	98(8.29)	89(90.82)	9(9.18)	
Sedation medication				
Dexmedetomidine+Chloral hydrate+Sevoflurane	74(6.26)	43(58.11)	31(41.89)	<0.001
Dexmedetomidine+Chloral hydrate	461(39.00)	434(94.14)	27(5.86)	
Dexmedetomidine+Propofol	269(22.76)	226(84.01)	43(15.99)	
Dexmedetomidine+Sevoflurane	186(15.74)	179(96.24)	7(3.76)	
Dexmedetomidine	40(3.38)	27(67.50)	13(32.50)	
Others	152(12.86)	96(63.16)	56(36.84)	

Table 3: Multivariate regression analysis of factors associated with adverse events.

Variables	Comparison	OR(95%CI)	P
ASA-PS class	III~	5.684(3.123,10.344)	<0.001
History of sedation	No	1.645(1.014,2.669)	0.044
Source of patient	Outpatient	3.379(1.873,6.097)	<0.001
Underlying diseases	Circulatory system	3.981(1.579,10.040)	0.003
Examination items	CT-enhance	75.534(27.101,210.521)	<0.001
	CT	8.104(2.011,32.664)	0.003
	MRI1.5	39.016(14.504,104.957)	<0.001
	Ultrasound	4.131(1.149,14.850)	0.03
Sedation plan	Intranasal+Oral	87.670(13.976,549.960)	<0.001
	Intranasal+Inhalation	243.166(15.045,3930.222)	<0.001
	Dexmedetomidine+Chloral hydrate+Sevoflurane	109.504(10.598,1131.414)	<0.001
	Dexmedetomidine+Propofol	253.751(5.321,12101.526)	0.005

Discussion

In our study, we found that sedation related adverse events occurred in 0.077% (177/229834) of all patients involved in the study, oxygen desaturation (40 cases), failed sedation (31 cases) were the most common events, with a low rate of SAEs (44 cases) in all patients. The results were similar to other studies [5].

Sedation for children's examination is essential, but is more vulnerable to respiratory depression and hypoxemia for the physiologic and anatomic differences in children. We found that most adverse events were categorized as respiratory including oxygen desaturation, airway obstruction, apnea, airway spasm and tracheal tube slip. Oxygen desaturation was the most common adverse events (40,22.60%), was consistent with other study [5]. At the meantime, the data may be understated because some physicians may administered supplemental oxygen at the start of sedation, whereas some provided when saturations less than 95%. Thus, saturations will not reach less than 90% and not considered as adverse events. In addition, a brief oxygen desaturations may not be considered adverse events by some physicians and they may not be recorded in the system [9]. They can be improved by interventions, like increasing oxygen concentration, bag-mask ventilation, the use of oral or nasopharyngeal airway and suction of secretions, few patients need intubation.

Circulatory diseases was an independent risk factor for adverse events (OR=3.981; 95%CI 1.579-10.040). There were 15 cases with arrhythmia, which underlying diseases mainly combined with circulatory diseases like congenital heart disease and arrhythmia. Of all the adverse event patients, 9 cases received intubation for sustain oxygen saturation, 12 cases were unplanned emergency admission. No death case happened as a result of complex underlying diseases. Careful evaluation, skilled technique and the preparation of rescue facilities are essential for them.

During the interval from July 2016 to Oct 2021, only 177 adverse events occurred in all. The low incidence of adverse events was mainly due to the participation of anesthesiologist specialists in our hospital, In the past, the sedation for children provided by non-anesthesiologists such as ward doctors, ICU doctors and emergency physicians [10,11]. A study of pediatric procedural sedation complication found that the total number of major complications lead by anesthesiologist (14 cases) was lower than those led by pediatrician (15 cases), emergency physician (30 cases) and intensivist (50 cases) [12], which is consistent with another study [3]. In addition, the use of propofol and sevoflurane led by anesthesiologist were associated with the high success rate of sedation, which were not available to non-anesthesiologists. Meanwhile, no cardiac arrest or death happened in the study.

In our adverse events, children under 3 years old had a high incidence of adverse events (78.53%), similar to other study [13], but there were no statistical significance across age groups. The ASA-PS class III was a independent risk factor for adverse events (OR=5.684; 95%CI 3.123-10.344); p<0.001), the higher the ASA-PS class, the higher the incidence of adverse events and and oxygen desaturation. Grunwell et al. found that ASA physical status III was associated with failed sedation, approximately twice as often as others [14]. Other study found ASA III to be a significant predictor for respiratory events [15]. The patients were mainly outpatients (OR=3.379; 95%CI 1.873-6.097). Grunwell JR found that the failed procedural sedation in children were happened on outpatients (73.5%) [13], for the outpatient's condition were unknown and there were many hidden diseases, they cannot be detected in time, and the sedation plan could only be set through simple medical history inquiry. Pre-sedation evaluation is very important. ASA-PS class III patients should be strict monitored and finish the examination accompanied by a doctor.

The sedation drugs mainly including Dexmedetomidine, Ketamine, Propofol and Chloral hydrate. Dexmedetomidine is commonly used in recent years. Intranasal Dexmedetomidine can provide adequate sedation for pediatric patients in non-invasive examinations [16,17]. The advantage is that it does not cause respiratory depression, but it can cause bradycardia when injected rapidly. 5 cases were found with bradycardia after procedural sedation. The incidence of SAEs was related to Dexmedetomidine and Dexmedetomidine combined Chloral hydrate with Sevoflurane, Dexmedetomidine with Propofol and Dexmedetomidine combined Chloral hydrate with Sevoflurane were related to adverse events, specially CT-enhance and MRI items, that of the longer duration of imaging and the contrast agent use as well as the increased need for patient immobility and cooperative, CT-enhance and MRI items require deep sedation, Propofol, because of its quick onset properties, remains the most favored agent in sedation, especially for radiologic examination [18]. Apnea and oxygen desaturation are known to occurred during propofol administration [19]. Interventions like mask oxygen, oral or nasopharyngeal airway and continuous positive airway pressure may not always be considered unplanned. The main reason for adverse events of CT enhancement is the use of propofol for sedation, and without oxygen supplement during the diagnostic test, Therefore, we need to monitor the patient's breathing and oxygen saturation to ensure patients' safety during the examination.

Limitations

There are several limitation to our analysis. Firstly, it was a single center retrospective study, and the adverse events sample size was small. Multiple center data are needed to confirmed the risk factors. Secondly, our adverse events included variability across examination, medications and physicians, with possible bias effect. Thirdly, we did not follow up the patients after discharged from the sedation center because adverse event could have occurred at home. Finally, all sedation was performed at an academic children's hospital, which may limit the generalizability of our results to in general hospitals.

Conclusion

In conclusion, children under 3 years old, ASA – PS class III, cardiovascular system disease, Dexmedetomidine combined with Propofol and Dexmedetomidine combined with Chloral hydrate and Sevoflurane are the risk factors of adverse events. This study is a single-center retrospective study with a small sample size, and a multicenter prospective study is needed to analyze the influence factors of adverse events in the further.

Declarations

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